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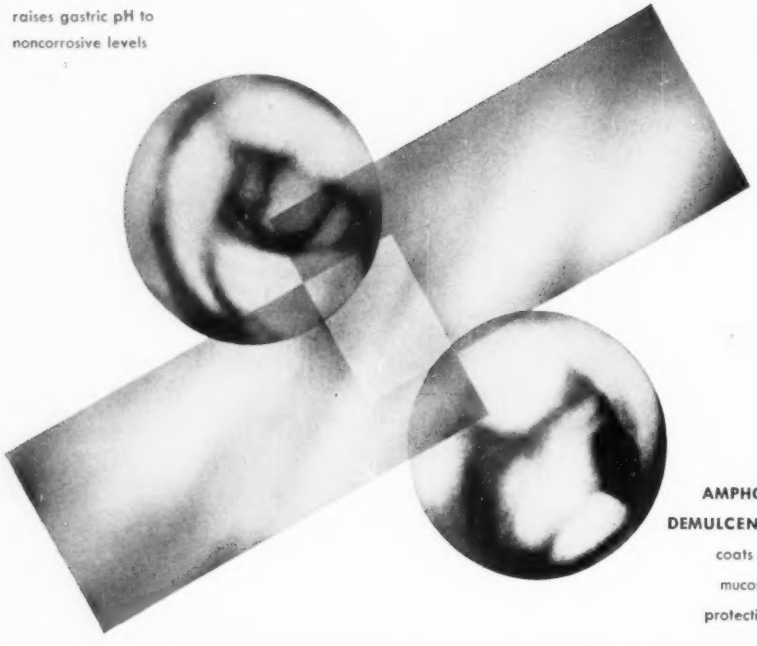

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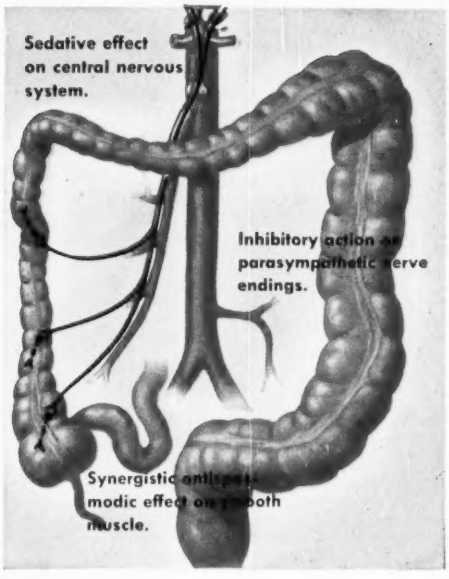
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1. Kammandel, N. et al.: Awaiting publication.
2. McGavack, T. H. and Klotz, S. D.: Bull. Flower Fifth Ave. Hosp., 9:61, 1946.
3. Weissberg, J., McGavack, T. H. and Boyd, Linn J.: Am. J. Digest. Dis., 15:332, 1948.

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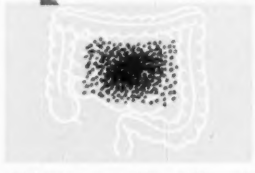

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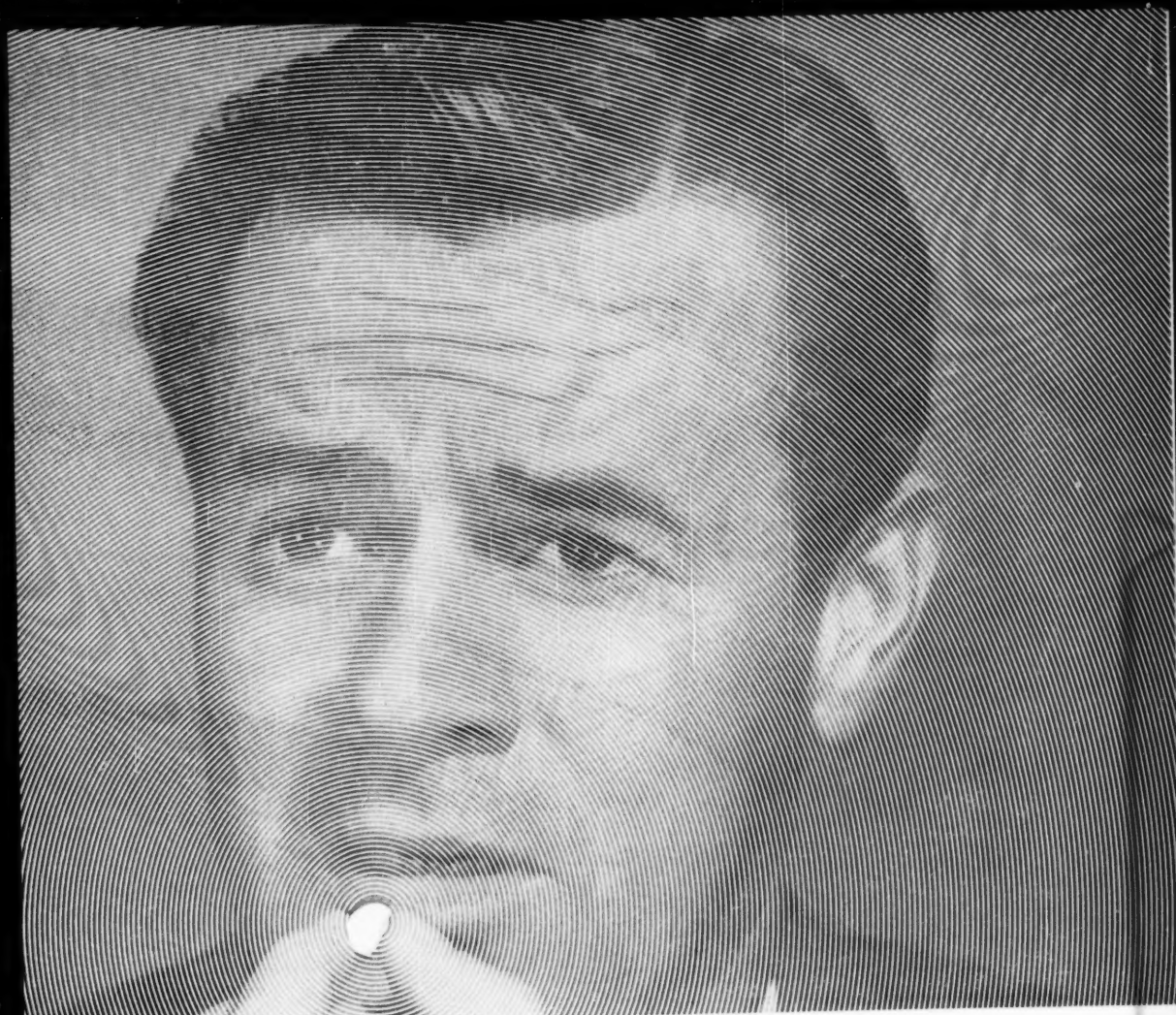

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1. Weiss, S., et al.: Rev. Gastroenterology 16:501-509 (June) 1949.

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A POLYAMINE FORMALDEHYDE RESIN*
IV. CLINICAL EVALUATION IN THE TREATMENT OF DUODENAL ULCER

HARRY L. SEGAL, M.D., HAROLD A. FRIEDMAN, M.D., ELDON E. ELLIS, M.D.** AND JAMES S. WATSON, JR., M.D.
Rochester, N. Y.

THE POSSIBILITY of the clinical application of synthetic ion exchange resins developed by Adams and Holmes (1) was suggested by the studies of Segal, Hodge, Watson, and Scott in 1945. (2) They found that the Amberlite IR-4† was able to neutralize the HCL of gastric juice resulting indirectly in the inactivation of pepsin. Preliminary feeding tests at that time showed that this resin was innocuous in the rat. In a later publication (1947) Segal and associates (3) showed that this resin was also essentially non-toxic when fed to rats over a period of eight months. In 1946 Martin and Wilkinson (4) confirmed the ability of Amberlite IR-4 to neutralize HCl. They found the resin to be non-toxic in rats, dogs, and human beings. In their work they used a much finer mesh size (200) of Amberlite IR-4 and noted thereby that the rate of acid neutralization per gram of Amberlite was greatly increased.

The use of this fine mesh resin in the treatment of peptic ulcer was reported in 1947 by Spears and Pfeiffer (5) and Kraemer and Lehman. (6)

These preliminary studies suggested that this fine mesh anion exchange resin was worthy of further clinical trial. Kraemer continued his interest in the clinical evaluation of this resin and described his results in a series of papers (7, 8, 9) in which eventually 82 ambulatory and 18 hospitalized duodenal ulcer patients received resin therapy. By and large he and his associates used this resin in capsule form in doses of 0.5 to 1.0 gm. every two hours alternating with two hour milk feedings. In the ambulatory group treated, 76 of the 82 patients remained symptom free from one to 17 months. Eleven of the hospital ulcer patients came to surgery and seven were improved by the resin regime. No side effects, as constipation, diarrhea, bloating, etc., were noted.

Further studies in the use of this anion exchange resin in the treatment of duodenal ulcer have been reported by Marks (10), Weiss, Espinal and Weiss (11), and J. Weiss (12). In the work reported in these papers, the resin was administered mainly in 0.25 gram capsules. The starting dose varied from 0.5 gm. every hour to 1 gm. every two hours. Occasionally the resin was given in doses as a powder (1 gram) mixed in water every two hours: night doses were variable and in the cases of J. Weiss, 1.5 to 1.0 gm. of the resin powder was given in milk at bedtime. Relief of symptoms occurred in 76% to 90% of the uncomplicated duodenal ulcer patients treated by these authors. No untoward side effects were observed.

J. Weiss (12) stated that 40 of his 44 ulcer patients had relief in one to eight days and that the ulcer niche disappeared in ten to fourteen days whereas the control patients required a longer period. The number of patients used as controls and the number of days required to heal the niche in these controls were not reported. The exact number of niches in his treated patients was not discussed.

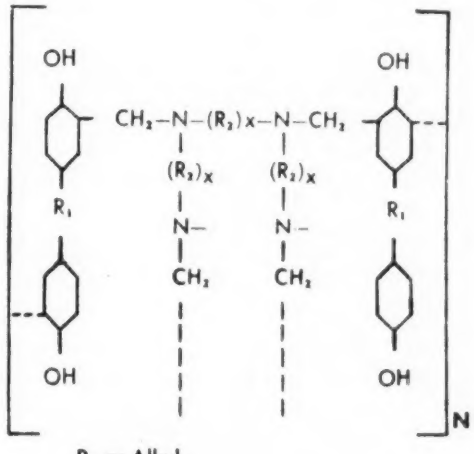

FIGURE 1.

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From the studies appearing in the literature, it can be stated that this anion exchange resin in the fine mesh size is (1) an efficient neutralizer of HCl in vitro, (2) produces no adverse effects when used clinically, (3) relieves ulcer symptoms, and (4) may indirectly hasten the healing of the ulcer.

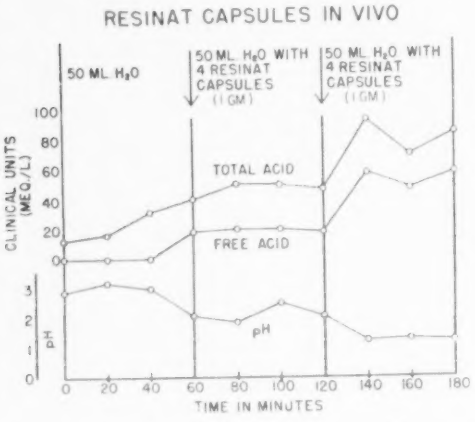
From the Departments of Medicine and Roentgenology, the Strong Memorial, the Rochester Municipal, and Genesee Hospitals—the University of Rochester School of Medicine and Dentistry, Rochester, New York.

*The resin used in the present study was supplied by the Medical Research Department of the National Drug Company of Philadelphia, Pennsylvania. This 200 mesh resin had been named Resinat by the National Drug Company and appears for the first time under that name in the work of Spears and Pfeiffer. (7) The capsules used in this study contained Amberlite XE-43, which has now been discarded. The resin now used in Resinat capsules is designated as Amberlite XE-58. It is a finer mesh resin and should be more efficacious than the capsules available for this study.

**Present address: Eldon E. Ellis, M.D. Department of Surgery, Stanford University Hospital, San Francisco, California.

†Amberlite IR-4 is a polyamine formaldehyde resin and its structural formula is suggested in Figure 1. (7)

It was thought by the authors that it would be of further value to learn: (1) what dose is effective in elevating the pH in the stomach to the point of pepsin inactivation, and (2) what therapeutic results would occur with such doses in patients with chronic duodenal ulcer of long standing.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50 ML. H_2O WITH 4 RESINAT CAPSULES (1 GM.)
CLINICAL UNITS (MEQ./L.)
TOTAL ACID
FREE ACID
pH
TIME IN MINUTES

FIGURE 2.

I. The In-Vivo Effect of Resin upon Gastric Acidity

Figure 2 demonstrates the average effect of resin in-vivo upon the pH, free acid, and total acid in a group of patients receiving the resin in capsule form. This figure reveals no significant effect from four capsules (1 gm.).

Figure 3 provides an example of the in-vivo effect of one and two gram doses of resin powder upon gastric acidity. One gram of this resin is not consistently effective in elevating the gastric pH. A two gram dose is practically constant in raising the pH from about 1 to 5 or 6.

II. Clinical Results

The clinical study in this work deals with the administration of this resin to 41 patients who had a history of chronic duodenal ulcer ranging from one and one half to twenty years. These cases were divided as follows (Table I): (1) Recurrent patients: those who had healed in previous episodes by the usual milk or milk and various antacid therapy; (2) Intractable cases: patients who had had no remission from pain for at least the preceding nine months in spite of adherence to a milk or milk and antacid regime; (3) Penetrating ulcers: patients with signs of peritoneal or pancreatic penetration with no relief by milk and other antacids; (4) Partial obstruction: patients with retention as shown by symptoms, intubation and x-rays.

The patients were considered to have had a clinical remission of their ulcer if pains disappeared within one or two weeks and if there was no recurrence of pains after cessation of the resin therapy. The regimen used consisted in the administration of resin every two hours with or without milk for one or two months; then milk every two hours was continued for about a month. Thereafter, the patient was requested to take one glass of milk between meals indefinitely.

The patients were classified as having had relief of symptoms if their pain was relieved only temporarily and/or recurred within one month after cessation of the resin therapy.

Summary of Results of Resin Therapy in Chronic Duodenal Ulcer Patients

Type of Duodenal Ulcer	Number of Patients	Clinical Remission	Temporary Relief	No Relief
Recurrent	26	17	3	6
Intractable	6	0	2	4
Penetrating	5	0	3	2
Partial Obstruction	4	0	0	4

TABLE I

The results are tabulated in Table I. Seventeen patients of the twenty-six classified in the recurrent group had clinical remissions. Three had only temporary relief and six failed to obtain any relief.

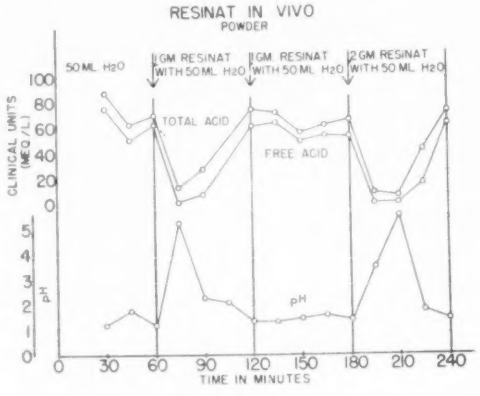

FIGURE 3.

The resin therapy failed to produce a remission in any of the complicated cases, although five patients had symptomatic relief.

Discussion

It would seem from the laboratory studies that the dose of this resin reported in the literature was insufficient to produce an adequate decrease in gastric acidity. Thus if the doses used actually relieved the symptoms and had a positive effect in hastening the healing of the ulcer, other explanations must be offered. Either the resin (1) eventually had a cumulative effect with an overall decrease in m. eq. of free HCl over a prolonged period of time, or (2) the

pH of the combined juices in the first part of the duodenum was elevated sufficiently to inactivate the pepsin, or (3) a combination of these factors came into play.

From the laboratory investigation shown here resin capsules were not effective in elevating the pH in the stomach. One gram of the resin powder did increase the pH in the stomach but two grams of the resin consistently attained elevation in the stomach pH above the level of peptic activity. The duration of the effect in the stomach was variable lasting from one to two hours. No acid rebound occurred.

Even though small doses of the resin may fail to raise the gastric pH above the critical level of 3.5, it is still possible that it may aid in keeping the duodenal pH above 3.5 and thus be a factor in alleviating symptoms and healing the duodenal ulcer. Kearney, Comfort and Osterberg (13) and Berk, Rehfuss and Thomas (14) have shown that the ability of the duodenal contents of the normal person to neutralize the gastric juice or chyme entering the duodenum may be impaired in the duodenal ulcer patient. This will allow free acid to contact the mucosa of the duodenal cap in the ulcer patient more frequently and for a longer period. That this resin may aid in elevating the pH in the first part of the duodenum above the critical level of a 3.5 is suggested by the studies of Wirts. (15) He has demonstrated that 30 minutes after histamine injection, the pH in the duodenum changes from 4.5 to 3.0 while that in the stomach decreases from 2.0 to 1.5. Under comparable conditions when 3.2 gms. of the resin powder was administered orally at the time of the histamine injection, the pH rose within 30 minutes to about 5.5 in the duodenum and to 3.0 in the stomach and within 60 minutes to 6.5 and 4.0 respectively. At the same time pepsin activity was considerably less in the duodenum than that in the stomach.

The difficulties in evaluating any therapy in a disease like duodenal ulcer are considerable. The tendency to spontaneous remissions, the influence of the emotions and other factors suggest caution in appraising the results. This has been aptly stated by Ivy, et al. (17) as well as by others. Thus any report of clinical studies on the effect of any antacid in the therapy of ulcer must be viewed in this light. The clinical results of resin therapy previously reported and the findings in this study can only suggest that this resin is able to relieve symptoms in uncomplicated duodenal ulcer patients and in some of the complicated ulcers and possibly can aid in the more rapid healing of the uncomplicated duodenal ulcer. It would seem that since there is no absorption of the resin and since there are practically no adverse side effects as diarrhea, constipation, etc., that when an antacid is necessary in the therapy of a duodenal ulcer case, this could be an effective agent.

Lopusniak and Berk (16) have reported the failure of milk to maintain the duodenal contents above the critical level of a pH 3.5. The combined use of an antacid as the resin with milk in the therapy of ulcer may attain such an end and would seem to be indicated especially in those patients in whom milk alone has failed to relieve the ulcer symptoms. It may also be an aid in those patients who cannot tolerate milk or comparable products.

The resin, as stated previously, failed to produce a remission in any of the complicated cases in this group. By and large there is no reason to expect an antacid to succeed in such cases.

It is realized that the treatment of duodenal ulcer as discussed here will probably change with the advent of drugs or other agents which may directly or indirectly inhibit the vagal gastric secretion or increase the mucosal resistance to ulceration or do both.

Summary and Conclusions

The literature concerning the use of an anion exchange resin in the treatment of peptic ulcer has been reviewed.

Laboratory data presented suggest that the average dose necessary to elevate the gastric pH consistently is 2 gm. of the powdered resin. Smaller doses may be efficacious because of the possible favorable effect upon the critical pH and pepsin activity in the first part of the duodenum.

A clinical remission of the ulcer symptoms occurred in 17 of 26 duodenal ulcer patients treated with this anion exchange resin. In three patients the symptoms were relieved only as long as the resin was used.

Relief of symptoms occurred in 5 of 15 patients with complications. No clinical remission took place in any of these 15 patients, all of whom came to surgery.

Practically no adverse side effects occurred with the administration of this resin.

This anion-exchange resin appears to be a useful antacid in the therapy of duodenal ulcer.

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THE NOXIOUS ANTRAL REMNANT IN TREATMENT OF PEPTIC ULCER OF THE DUODENUM

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UNTIL an "Anti-ulcer" treatment is developed and made clinically applicable, the aim of treatment of peptic ulcer is to eliminate (or markedly reduce) the secretion of hydrochloric acid. This has been attempted by many indirect and few direct means, none of which have been entirely satisfactory. A study of the constantly changing surgical treatment of duodenal ulcer reveals: among other things, strikingly improved results coincidental with removal of more and more proximal (acid secreting) stomach, as is to be seen after the presently accepted subtotal (distal) gastrectomy.

In a recent article, the post-gastrectomy stomach was spoken of as a "Restored" stomach, but with longer follow-ups, the restoration is questionable. The stomach is mutilated and the patient is sometimes, what might be called, a gastric cripple because of jejunitis, stomal ulcer, gastro-jejuno-colic fistula, retrograde intussusception, mal functioning stoma or the so-called "post-gastrectomy" or "Dumping" syndrome. These, in turn, have led to various less extensive, more physiologic procedures in attempts to improve results, such as: Vagotomy, total (Dragstedt) (1); Jejunal Transplantation (Andrus et al) (2); Gastric devascularization (Somerville and others) (3); Partial (proximal) gastrectomy—Fundusectomy (Connell) (4).

Total Vagotomy is still on trial with less enthusiastic approval after longer follow-ups.

Jejunal transplantation was not accepted.

Devascularization was unsatisfactory. Evaluation of its results is difficult as it was accompanied by gastro-jejunostomy.

All of this would seem to justify a discussion of the presently accepted *distal* subtotal gastrectomy and of the contrasting *proximal* subtotal gastrectomy (partial fundusectomy) and the suggestion of a more extensive (or total) fundusectomy, with cardia-antral anastomosis.

Before doing so, attention should be directed to the fundamental importance of differentiation between peptic ulcer of the stomach and of the duodenum. The latter is now recognized as a general disease with a local lesion, to be treated by non-operative management, except for complications such as acute perforation, organic obstruction, so-called "intractability" and sometimes hemorrhage. The same principles do not necessarily apply to gastric ulcer, because of malignant potentialities and other differences.

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It should be emphasized that surgery is not an end in itself, but merely an incident, often most important, between pre- and post-operative treatment, the latter to continue indefinitely.

Reduction of gastric acidity has usually been accomplished by neutralization or *indirect* methods, but comparatively little attention has been given to the other, seemingly more rational, horn of the dilemma, viz. *direct* removal of the acid secreting mechanism.

The presently accepted subtotal (distal) gastrectomy, with emphasis upon removal of the entire antral mucous membrane, is based essentially upon the theory of Edkins (5) i.e. that the antral mucosa secretes an alleged hormone, "Gastrin" which is carried into the fundus and stimulates the secretion of hydrochloric acid. This theory was presented in 1906 and has not been proven by physiologists or clinicians. In 1941 I discussed this theory (6).

But granting, for argument's sake, the existence of the hormone "Gastrin" (not histamine), its obliteration by antral resection would reduce secretion of hydrochloric acid by but a *fraction*, as at least three other important stimuli remain intact, viz. nervous (psychic, vagal), gastric remnant (chemical, mechanical) and intestinal.

The importance of a distinction between "Gastrin" and histamine is the possibility that histamine, or an "histamine-like" substance may originate elsewhere than in the antrum.

In view of "Nature's" well known propensity to establish many compensatory mechanisms, it would seem reasonable to expect the histologically similar duodenal glands of Brunner to "carry on" for the removed antral glands. Their chief difference seems to be in their relationship to the submucosa as Kahlson (7) pointed out.

It would seem possible that an "histamine-like" substance derived from the intestine or from the amino acid, histidine of practically all protein, might serve as a substitute.

Under the title, "Histamine and Gastric Secretin in Relation to anti-histamine Drugs," Ivy (8) states, "Although the final word is yet to be spoken, the weight of evidence now available indicates that histamine is not "gastrin" and that histamine may be released by the gastric and intestinal mucosa only when the mucosa is irritated mechanically or chemically." Alvarez (9) says "I can agree with you that the modern operations for ulcer are all unsatisfactory, and

I am afraid of all of them. I am not up on all the literature of gastric secretion, but my impression has been that the Edkins theory has been pretty well exploded."

The dramatic "Cure" of a few jejunal or stomal ulcers after removal of the so-called "noxious antral remnant" has led to enthusiastic recommendation of antrumectomy by practically all writers on the surgical treatment of duodenal ulcer. This recommendation persists in spite of the fact that in the evolution of surgical treatment of duodenal ulcer, removal of the *antrum alone* was not satisfactory. Good results did not follow until resection in a "shift to the left" (10) passed through pylorectomy, antrumectomy, partial to "subtotal gastrectomy" which has been generally accepted.

Removal of the antrum is still advocated, despite the many cases of *prolonged remissions* in which the antrum and the sphincter remain (after proximal resections, other procedures, various non-operative treatments, and even after *no treatment*.) It is advocated with disregard of the loss of alkaline mucous secretion (one of Nature's buffers which may contain Castle's intrinsic factor); and despite the many physiologic malfunctions following the abnormal gastrointestinal continuity and the loss of the pyloric sphincter mechanism, with consequent unregulated exposure of non-adapted jejunal mucous membrane to the acid peptic chyme.

Nature's postoperative attempt at sphincter action at the stoma may sometimes be seen at fluoroscopy.

Disturbance with, or destruction of, other sphincters e.g. pharyngeal, oesophageal, biliary or urinary, disturb normal function and produce clinical symptoms. The consequences of loss of control of the anal sphincter are very evident and deplorable. Loss of control of the pyloric sphincter may be followed by serious digestive disturbances, even if not equally apparent. The opposite condition, pylorospasm or stenosis, certainly causes recognizable signs and symptoms.

One is impressed by the frequent failure of distal resection and by the satisfactory results following a third and even a fourth removal of more and more of the acid secreting fundus. It seemed that the "noxious remnant" might be fundal rather than antral and suggested the query, Why not do the last operation (proximal gastric resection—total 98% fundusectomy) first? Ivy (11) said, "Removal of the antrum is only necessary when a considerable portion of the parietal cells are left in situ." This more physiologic procedure might gain the *advantages* of subtotal gastrectomy (diminish acid secretion) without the *disadvantages* of loss of alkaline antrum secretion and sphincter mechanism. In an attempt to answer the above question, I have performed partial gastrectomy (fundusectomy) in 25 clinical cases (4). The results have been 16 favorable and 9 unfavorable, not above the average, for intractable cases. The tonicity and motility seem not to be interfered with, the size and shape gradually return to normal, the secretion of hydrochloric acid, at first reduced, returns to normal, indicating insufficient removal of proximal stomach.

Dr. Blake Fawcett of Duke University (12) made this pertinent observation, "Several investigators have reported on the routine gastric analysis following fundusectomy, but I have not found a report on the total gastric secretions or on the proteolytic activity of the gastric secretions before and after fundusectomy. It is entirely reasonable that the proteolytic activity may be reduced far greater than the free or total acids." Judging from an analogous condition, hyperthyroidism, in which poor results, after earlier limited resections of the thyroid gland, were definitely improved by extensive subtotal resections; it might be that with removal of more of the hydrochloric acid secreting area, by a sleeve resection with cardia-antral anastomosis, the results might, likewise, improve.

Recently a reconsideration of the subject has been recommended, e.g. Ricketts et al (13) says (p803) "It is interesting to note that Brick, after delivering huge doses of 5000 or 6000 r to the gastric antrum in tumor therapy observes *no change* in the gastric secretion. This observation might be used as an argument against the existence of a pyloric organ elaborating a hormone which stimulates the acid secreting glands in the upper half of the stomach."

Kirsner et al (14) after reporting Case 5 (p 609) comments (p 612) as follows: "This patient manifested a truly intractable tendency to ulcer formation. The marked hypersecretion and development of a jejunal ulcer several weeks after partial gastrectomy and removal of the mucosa from the *duodenal bulb* is of particular importance in view of the renewed interest in resection of the antrum for treatment of peptic ulcer."

CONCLUSIONS

Until some "anti ulcer" medicament, hormone or biologic extract similar to Enterogastrone, Urogastrone or Anthelon is developed and made clinically applicable, the objective of treatment remains diminution of, or elimination of hydrochloric acid from the gastric content.

In Mann-Williamson dogs (where the acid secreting parietal cells are distributed throughout the entire gastric mucosa) stomal ulcer develops after "subtotal" gastrectomy, but does not do so after total (98%) gastrectomy (15).

In man (with the acid secreting cells usually limited to the proximal two-thirds of the stomach) removal of the alkaline secreting distal antrum is therefore unnecessary in an attempt to reduce hydrochloric secretion.

Because of the disadvantages of distal resection, and because of the "pari passu" improvement with more and more proximal resection (shift to the left) it may be that the fundal remnant after subtotal gastrectomy, is more "noxious" than an antral remnant.

Total fundusectomy (proximal partial gastrectomy) with removal of practically all (98%) of acid secreting fundus and body with anastomosis between the cardia and the alkaline secreting antrum would seem to be a logical physiologic improvement in the treatment of peptic ulcer and worthy of a clinical trial in surgical treatment of duodenal ulcer.

Removal of the secreting apparatus, the parietal cells, would permit a disregard of the various indirect (hormonal neural, cerebral, gastric or intestinal) stimuli to hydrochloric acid secretion, *retain* the advantages of the presently accepted "subtotal" gastrectomy (reduction of hydrochloric acid secretion) while *avoiding its disadvantages* (stomal ulcer, the post-gastrectomy

or "dumping" syndrome) that sometimes follow the unphysiologic gastrojejunal continuity and loss of alkaline secretion.

Possible objections are that the ulcer remains (removal may be unnecessary if the cause is removed) and pyloric obstruction, if functional will, of course, be corrected in pre-operative management; if organic, retention may be relieved by an associated pyloroplasty or gastro-duodenostomy.

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INDUCTION OF NORMAL DEFECATION REFLEX BY DISTENTION OF THE RECTAL STUMP FOLLOWING REMOVAL OF THE RECTO SIGMOID

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THIS report concerns observations on the mechanism of defecation in relation to the anatomical conditions resulting from resection of the recto sigmoid colon for removal of cancer.

NORMAL DEFECATION REFLEX FOLLOWING DISTENTION OF CLOSED RECTAL STUMP

It is known that the act of defecation is an intestinal gradient. This has been proved by physiological experimentation. The nerve fibers involved in the reflex mechanics for defecation are derived from 2-3-4-5 lumbar and 1-2-3 sacral. This reflex is initiated by intestinal gradient and fecal contents cause a local distention and irritation of the rectal wall. Once the urge for defecation has been initiated, the reflex is completed by impulses through the sympathetic nerves causing relaxation of the sphincters and stimulation of contractions of the bowel musculature. Contraction of accessory abdominal muscles resulting as a sequel of the reflex induces expulsion of fecal contents. Abnormal defecation takes place if injury, disease, or operative procedure involves any one of these factors.

REPORT OF CASES OF THE NORMAL DEFECATION REFLEX THROUGH THE COLOSTOMY OPENING BY STIMULATION OF RECTAL STUMP

A. J., age 34, was seen July 24, 1941, with symptoms of severe pain in lower abdomen, coming in waves. The condi-

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tion had started a year previous with periods of bleeding from the rectum. There was some bleeding with bowel movements and once a rather severe hemorrhage. Several weeks before the patient was seen, he had an attack of severe pain, fever, and high white blood count. He was hospitalized and this attack slowly subsided under sulfonamide therapy.

Diagnostic Procedures

Barium enema showed that the barium did not advance farther than the recto sigmoid junction where there was a deformity characteristic of cancer of the recto sigmoid. Figure 1 shows this cancer of recto sigmoid before operation.

Sigmoidscopic examination showed a cauliflower cancer of the recto sigmoid, thirteen centimeters from the anal orifice. Biopsy confirmed this diagnosis.

Operation

Hartman's anterior resection of recto sigmoid, under continuous pontocaine glucose spinal anesthesia, was performed. Exploration showed no tumor metastasis to the liver. The omentum was adherent to the recto sigmoid lesion. The omentum showed a granular appearance which was considered not to be metastatic. There were a few palpable glands in the recto sigmoid mesentery which were removed with the resection.

The tumor was located in the recto sigmoid. The cancer showed evidence of having perforated with abscess formation. With difficulty, the tumor was mobilized far enough to put a right-angle clamp below it and to remove it. The rectal stump was inverted and sutured by interrupted chromic stitches. Mesentery was closed above the rectal stump by continuous chromic sutures and the rectal stump was drained by a No. 16 rubber catheter extraperitoneally. The tumor was removed by cautery and the distal end of colon put out through the incision as a permanent colostomy. The incision was closed by interrupted figure eight with No. 32 steel alloy wire. Clips were placed in the skin.

Fig. 1

The Hartman's anterior resection of the recto sigmoid was done due to the fact there had been a purulent infection at the time of the operation and it was considered unwise to do a combined resection because of the spreading of the infection. It also was considered unwise to perform a primary anastomosis in an infected pus area. The type of the Hartman anterior resection was thought to be the procedure of choice. The patient made an uneventful recovery following surgery.

Gross Pathological Description

"The tumor mass is annular, involving the entire circumference of the colon in places, seven cms. in length . . . The surface is in great part ulcerated and in places there is reddish brown discoloration of the tumor tissue extending through the entire thickness of the wall with fibrinopurulent exudate covering the serosa here. Above the tumor mass the muscular coats appear thickened and hypertrophied."

Microscopic Description

Microscopic description confirmed the diagnosis of annular adenocarcinoma of the colon with peritonitis.

Discussion and Results

The patient has now been followed eight years after the surgical removal of the tumor and so far no recurrence of cancer has been found.

On his return visits he has always stated that if he wished to have his bowels move from the colostomy opening he would take a small enema of about 300 c.c. of saline in the rectal stump and in a short period this stimulation would cause the peristalsis of the remaining colon, resulting in a normal bowel movement. In the face of the absence of the recto sigmoid removed by previous surgical measures, barium enema was performed, as seen in Figure II. The rectal stump was filled with 300 c.c. of barium. In two minutes a bowel movement of normal type was evacuated through the colostomy opening.

CASE 2.

J. E. S., age 40, was first seen April 12, 1947, with symptoms of distress in the lower abdomen and marked constipation, also a loss of thirty pounds in weight. His complaints had started about a year before his appearance for diagnosis. After

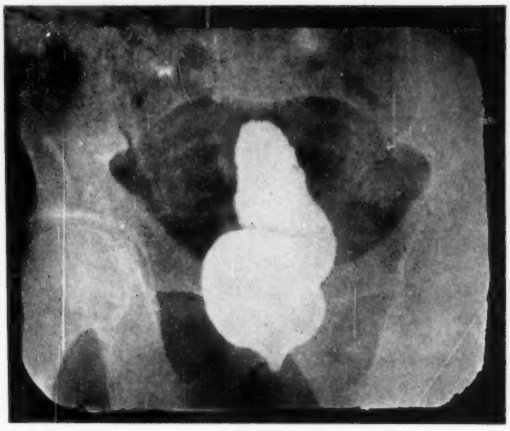

Fig. 2.

thorough study, barium enema (Fig. 3) showed a marked deformity characteristic of the advanced carcinoma of this area. The patient was operated on September 24, 1947, at which time the tumor of the sigmoid was considered inoperable because of metastases to the lateral pelvis and because it was fixed firmly to the curve of the sacrum. Therefore, a colostomy was performed.

The patient wished to avail himself of all possible aid that could be gained from deep x-ray therapy. Following two

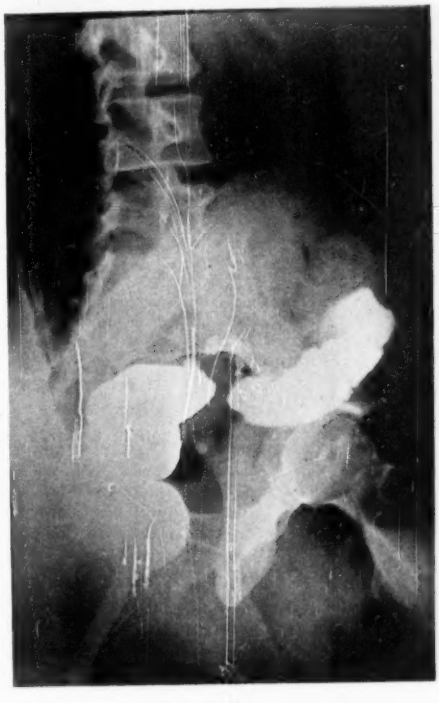

Fig. 3.

months of such therapy, the second operation was performed on September 24, 1947, at which time the cancer of the recto sigmoid was removed with the greatest of difficulty. Because the operation was considered only a palliative procedure the Hartman method of anterior resection of the recto sigmoid was performed. The patient made a good recovery after this operative procedure.

At a later period of time the rectal stump was examined by sigmoidoscope and there was found no metastases. To get a better idea of the size of the rectal stump a barium enema was given about 200 c.c. Three minutes after the enema the patient's bowels moved from the permanent colostomy, confirming in the second case the fact that peristalsis through the residual rectal stump stimulated the sacral nerves to the descending colon.

CONCLUSION

This is a report of two cases of cancer of recto sigmoid, following Hartman's anterior resection, whereby distention of the rectal stump with fluids resulted in evacuation of the colon through the permanent colostomy opening.

This shows in human cases, the proof of animal experimentation of the nervous spinal cord mechanism involved in initiation and control of the act of defecation.

EFFECT OF CYTOCHROME C AND SODIUM SUCCINATE IN CASES OF CHRONIC HEPATIC DISEASE

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A RECENTLY reported (1) case of hepatolenticular degeneration was found to have evidence of tissue hypoxia, and was treated with the respiratory enzymes cytochrome c and sodium succinate, with resulting clinical and laboratory improvement. After four months of continuous therapy, the patient developed eosinophilia, cytochrome c was discontinued, and prompt relapse occurred, with death following aspiration pneumonia. At autopsy, the typical nodular Laennec cirrhosis of the liver was found microscopically to have an unusual degree of active regeneration, such as is seen in healing acute yellow atrophy. Proliferation of bile ducts was pronounced throughout and suggested an adenomatous process in some areas. The parenchymal cells showed remarkable variation in configuration and staining, many were of huge size, and a high percentage showed two or more nuclei.

Soon after our experience with this case, Drabkin (2) reported that injections of cytochrome c in partially hepatectomized rats resulted in 25% greater regeneration of liver tissue than in controls, both groups being maintained on a high protein diet.

In view of these suggestive findings, it appeared desirable to test the effect of cytochrome c and sodium succinate in cases of chronic hepatic disease showing evidence of hepatic insufficiency, in the hope of stimulating regeneration of hepatic parenchyma with possible improvement in hepatic function.

Material and Method. Six cases of chronic hepatic disease were selected. All showed anatomical changes on biopsy, four of Laennec cirrhosis, one of intrahepatic cholangiolitic cirrhosis, and one of chronic infectious hepatitis. Liver function impairment varied from slight to severe. Every case was maintained on a high protein, high carbohydrate, low fat diet, containing 140 grams of protein daily. Actual consumption of food offered was not calculated, but supplemental protein beverages and intravenous protein hydrolysates were used when intake was considered inadequate. Supplementary medication in all cases consisted of daily multivitamins, brewers' yeast 15 grams daily, methionine 3 grams daily, and, in those cases which showed fat infiltration on biopsy, choline 3 grams daily. A low salt intake, and occasional mercuhydrin injections, were used when edema or ascites was present (cases 1, 5 and 6). At approximately monthly intervals, the anatomical and functional liver status was estimated by needle biopsy and the following laboratory tests: serum albumin and globulin, cephalin cholesterol flocculation (Hanger), thymol turbidity (Maclagan), bromsulfalein retention (5 mg. per Kg. at 45'), serum cholesterol and esterified fraction (Sperry-Schoenheimer), direct reacting 1 minute and total bilirubin (Ducci-Watson), alkaline phosphatase (Bodansky), prothombin time (Quick), and urine urobilinogen (2 hour semi-quantitative Ehrlich reaction, on three successive days).

Each case was followed for a number of months until maximal improvement and stabilization had occurred clinically, histologically and functionally. Then cytochrome c and sodium succinate were added to the basic regimen. Cytochrome c was administered in solution intramuscularly b.i.d. in dosage of 100 mg. daily in all but case 5. This case received a modified schedule consisting of 100 mg. daily for 10 days, 50 mg. daily for 10 days, 50 mg. every other day for 10 doses, and 50 mg. twice weekly for 20 doses. Case 1 received a total of 3.7 Gm. of cytochrome c, cases 2, 3 and 5 received 3.0 Gm., case 4 was terminated after 0.8 Gm. because of allergic reaction, and case 6 was terminated after 1.2 Gm. because of lack of supply. Sodium succinate was administered orally in dosage of 3.0 Gm. daily during the administration of cytochrome c, and was continued as long as the cases remained under observation.

Our preparation of cytochrome c was purchased from a reliable laboratory (The Treemond Company, New York) as a lyophilized product, which we dissolved and sterilized by Seitz filtration. It was prepared from equine hearts. Case 4, who developed fever and inflammatory induration at the site of cytochrome

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c injections, was found to be allergic to horse serum, which may have been present in traces in the preparation. The preparation furnished us assayed spectrophotometrically as 96% cytochrome c, and 99% by enzymatic reduction of cytochrome oxydase.

Our criteria for evaluating regeneration in hepatic parenchymal cells followed the description of Ashworth and Reid (3): "The most characteristic change consisted of enlargement of the nuclei, with greater variation in shape than normal, often being oval, but usually rounded, and sometimes quite irregular. These enlarged nuclei were characterized by increased chromatin and larger and more numerous nucleoli. Many of the regenerating live cells were binucleate. Mitoses were not seen, except in a single case, and cell division was believed to occur by amitosis or by polyploidy, a phenomenon of karyokinesis occurring in binucleate cells. The cytoplasm of regenerating cells was increased in amount, and was usually more opaque and pale than normally. These regenerating hepatic cells occurred within the lobular structure, and there was no evidence of their producing lobular distortion." The more commonly recognized nodular form of hyperplasia of the cirrhotic liver presumably follows upon destruction of the vascular supply or the reticular framework of the liver lobule.

Protocols. Case 1. A 58 year old unmarried white male housepainter had a lifetime history of alcoholism, with a poor nutritional history. Acute alcoholic hallucinosis had occurred ten years previously. Abdominal distress and indigestion had been present for the past 19 years. Ascites appeared in June 1947, requiring hospitalization and frequent paracenteses from that time until death in January 1949. The recurring abdominal distention resulted in development of large umbilical and left femoral hernias. Following paracentesis, the liver and spleen could be palpated, the former 7 cm., the latter 6 cm., below the costal margins, both being smooth, firm, and not tender. There were atrophic changes in the skin and musculature, labored respiration, weakness and tremor. Moderate bilateral gynecomastia was present, the testes were atrophic, and the body hair scant. There was edema of the sacral area and legs, and deep pigmentation and varicosities of the lower legs. The skin showed numerous hemangiomata

TABLE 1
LIVER FUNCTION STUDIES IN RELATION TO CYTOCHROME C THERAPY

			BSP	BILIRUBIN		PASE	CEPH. FLOCC.	THYMOL TURB.	ALB.	GLOB.	CHOLESTEROL		PROTH.
			%	TOTAL mg.	I' mg.				Gm.	Gm.	TOTAL mg.	ESTER %	TIME Sec.
CASE 1 — CYTOCHROME c 3.7 Gm. — JUNE 4 — JULY 22	JUNE	11	20	1.2	0.2	4	2	3	3.1	2.2	204	59	16
		24	32	1.1	0.1	8	0	3	3.3	2.4	146	58	15
	JULY	6	36	0.8	0	7	3	2	2.7	2.6	200	50	14
		22	23	0.8	0.2	5	2	4	3.2	2.6	178	73	15
	AUG.	23	18	0.7	0.2	5	0	3	3.2	2.0	182	67	16
	OCT.	4	13	0.8	0	5	1	9	3.4	2.7	196	53	15
	NOV.	4	31	1.0	0.2	5	3	6	3.7	2.5	192	59	15
CASE 2 — CYTOCHROME c 3.0 Gm. — AUG. 6 — SEPT. 5	JULY	29	10	0.4	0	5	0	3	4.8	2.4	318	71	17
	SEPT.	7	2	0.8	0	9	0	6	4.4	2.5	238	65	14
	OCT.	7	3	0.9	0	7	0	5	4.2	2.4	234	63	14
	NOV.	8	15	0.3	0.1	7	0	3	5.0	2.5	242	59	15
	JAN.	4	12	0.4	0	3	0	3	4.2	2.8	207	63	17
CASE 3 — CYTOCHROME c 3.0 Gm. — OCT. 13 — NOV. 12	OCT.	13	25	25.0	13.5	51	4	15	4.1	3.3	208	56	15
	NOV.	12	40	23.5	11.5	29	4	18	4.3	3.2	204	49	17
	DEC.	13	49	21.5	11.0	20	4	14	3.9	3.2	258	54	14
	JAN.	17	65	25.5	11.5	57	4	23	4.3	3.4	267	55	19
	FEB.	24	55	20.0	9.0	54	4	16	4.4	2.9	246	61	13
	APR.	27	53	10.1	2.2	42	4	15	4.1	3.1	208	58	14
CASE 4 — CYTC 86mg. — DEC. 1-8	NOV.	16	12	0.6	0.1	3	1	9	3.9	2.3	375	55	15
	DEC.	22	36	0.6	0.2	6	1	7	5.0	2.1	370	56	14
CASE 5 — CYTOCHROME c 3.0 Gm. — DEC 4 — MAR 22	NOV.	15	11	0.6	0	3	2	12	4.3	3.3	171	63	17
	DEC.	22	18	0.8	0.2	6	0	8	3.9	3.5	186	66	17
		29							4.9	2.7			
	JAN.	24	18	0.5	0.1	6	0	11	4.6	3.2	242	58	14
	MAR.	1	17	0.6	0	7	0	9	4.5	2.7	192	61	14
	APR.	4	20	0.7	0.1	7	0	8	4.2	2.7	200	62	12
	MAY	4	15	0.9	0.4	8	0	7	4.4	3.1	202	63	14
	MAY	31	18	0.5	0	3	0	7	4.3	2.9	240	58	14
CASE 6 — CYT. c 1.2 Gm. — FEB. 26-MAR. 11	FEB.	7	9	0.5	0	9	0	8	4.9	2.6	344	59	14
	APR.	25	4	0.8	0	9	0	6	4.4	2.7	272	61	14
	JUNE	22	6	0.8	0	6	0	5	4.0	3.3	260	63	13

Table 1. Liver function studies in relation to cytochrome c and sodium succinate therapy. The initial study in each case is representative of a stabilized status achieved on the standard hepatic regimen, prior to the added enzyme therapy. Inclusive dates of cytochrome c administration, and the total quantities administered, are indicated in column 1. Sodium succinate therapy was concurrent with the use of cytochrome c and continued through the period of observation.

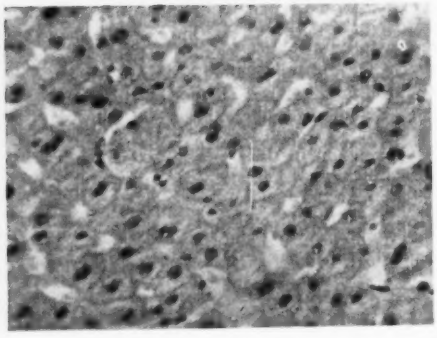

Fig. 1a. Areas of parenchymal cells from liver biopsies, case 1, June 11, following stabilization on a hepatic regimen, and prior to enzyme therapy. H. and E., x240.

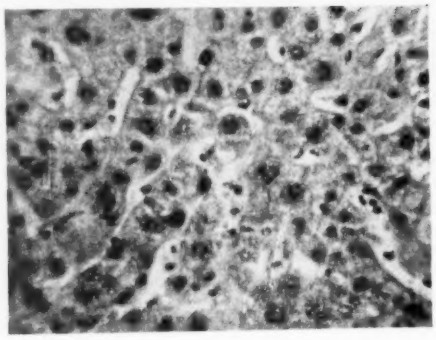

Fig. 1b. July 22, following 37 days of cytochrome c and sodium succinate. Note increased size and variability of nuclei with frequent double nucleated cells. H. and E., x240.

and spider nevi, and there was marked dilatation of the veins of the anterior and lateral abdominal and thoracic walls. Esophageal varices were not found roentgenoscopically, and there was no history of hematemesis. A functioning gallbladder contained a solitary stone. Moderate hypochromic anemia and elevated sedimentation rate were constantly present. Urinary urobilinogen was occasionally increased. The liver function tests are listed in Table I.

Liver biopsies showed characteristic periportal cirrhosis of the Laennec type, with distorted lobular architecture, increase in fibrous tissue particularly in the periportal areas, lymphocytic and some polymorphonuclear cell infiltration of the fibrotic areas, bile duct proliferation, and slight hepatic cell regeneration. Following cytochrome c and sodium succinate therapy, considerable hepatic cell regeneration appeared (Fig. 1, a and b). There was greater variation in size and staining of the hepatic cells and their nuclei, some of which contained multiple nucleoli. Double nucleated cells were numerous, and one triple nucleated cell was seen. Bile duct proliferation did not increase further.

The enzyme therapy effected no change in the rate of formation of ascitic fluid. Incarceration of the umbilical hernia occurred, necessitating surgical relief, which was followed by gradual hepatorenal failure and death within three weeks. The patient had been under observation for eighteen months.

Autopsy revealed the characteristic late stage of Laennec cirrhosis of the liver, which weighed 1150 grams. Considerable regeneration was evident in the parenchymal cells, probably attributable to the stimulus of terminal hepatic failure rather than to a continued late effect of enzyme therapy. Esophageal varices were found. The spleen weighed 700 grams.

Case 2. A 52 year old white married male cook had been a chronic alcoholic for over 20 years. In 1945, he developed anorexia, weight loss of 25 pounds, weakness, jaundice lasting 3 months, transient alcoholic psychosis, peripheral polyneuritis, ascites, and unilateral gynecomastia. After 26 paracenteses, the ascites was adequately controlled by mercurial injections and a low salt diet, and finally disappeared in 1946. Spider varicosities were present, and the liver edge was palpable 6 cm. below the costal margin, smooth, firm, and tender. Response to a high protein diet with supplemental vitamins, methionine and choline, was excellent, except for periods of alcoholic relapses, for which he was repeatedly hospitalized. He was continuously hospitalized from March 1948 until completion of the present study the following January. Spider varicosities, hepatomegaly, and peripheral neuropathy were constantly present; the spleen was not enlarged. Esophageal varices were not found, and there was no history of hematemesis. Routine blood and urine studies were normal, but the urinary urobilinogen was occasionally increased, and the sedimentation rate was always moderately elevated. The liver function tests are listed in Table I.

The liver biopsies showed characteristic periportal cirrhosis of the Laennec type, with distorted lobular architecture, periportal fibrosis, lymphocytic infiltration in the periportal areas, and bile duct proliferation. Following cytochrome c (August 6 to September 5) and sodium succinate therapy, moderate hepatic cell regeneration became evident, with greater variation in size and staining of the hepatic cells, and frequent double nucleated cells. The regeneration was maximal October 7, but still persisted in the last biopsy January 4.

Case 3. (Kindly referred for this study by Dr. Don C. Wakeman). A 21 year old single white male student had chronic ulcerative colitis, hepatic cirrhosis, and rheumatoid arthritis. His illness had begun at the age of 13, when a severe sore throat, which was treated with sulfonamides, was soon followed by a watery diarrhea, and six weeks later by jaundice. Jaundice and diarrhea have been present constantly since then, despite continuous therapy at many clinics. Intermittent attacks of rheumatoid arthritis first began during a course of Bargen vaccine therapy at the age of 16.

Body development was retarded, with sparse body hair and beard, and feminine type pubic hair. The breasts were enlarged and tender, and the testes were atrophic. There was cyanosis and marked clubbing of the fingers and toes, and the lower legs were edematous. There was diffuse involvement of the peripheral joints, which were swollen, warm and tender; slight dorsal scoliosis and lumbar straightening were present. The heart was small, with heaving rapid pulsations, and a systolic murmur, attributed to anemia. The lower chest and upper abdomen showed marked prominence, due to hepatosplenomegaly. The liver and spleen both measured 12 cm. below the costal margins, and were smooth, firm, and slightly tender. No ascites or dilated veins were found. There were no neurologic changes.

There was a constant moderate hypochromic anemia and intermittent eosinophilia, unaffected by therapy. The urine constantly showed bile and traces of albumin. The arteriovenous oxygen difference was normal. Esophageal varices were found on roentgenoscopy, but there was no history of hematemesis. The liver function tests are listed in Table I.

Therapy had consisted of high protein diet, choline, methionine, brewers' yeast, vitamins, ferrous sulfate, occasional transfusions, and sulfonamides. Cytochrome c and sodium succinate were added October 13. Symptomatic improvement occurred by early November and continued until April 27, when observation was discontinued. Weight gain of 10 pounds had occurred by that date, an unusual event in this emaciated patient. The liver and spleen became progressively smaller, being 10 and 8 cm. below the costal margins in November and December, 8 and 7 cm. respectively on April 6, and 6 and 4 cm. on April 27; this progressive change was confirmed roentgenologically (4). The acute phase of arthritis subsided by January. Diarrhea and jaundice (see bilirubin figures in Table I) improved progressively.

The liver biopsies were compatible with intrahepatic cholangiolitic cirrhosis of advanced degree. The greater part of all specimens consisted of connective tissue, with dissociation and degeneration of parenchymal cells, and infiltration with lymphocytic, endothelial, and polymorphonuclear cells. The gross specimens were deeply bile stained, and microscopically the parenchymal cells showed bile pigment retention, and the biliary canaliculi contained plugs of inspissated bile. Edema in the small parenchymal nodules was present prior to cytochrome c and sodium succinate therapy, but absent thereafter. Maximal regeneration was obtained January 5, was slight in degree, but persisted in the last biopsy taken March 1. It was characterized chiefly by increase in double nucleated cells.

Case 4. A 54 year old white male housepainter had had three episodes of painless jaundice, accompanied by dark urine and light stools, in 1930, 1946, and 1948, each attack lasting two months and subsiding gradually. His nutritional history was good, and there was no weight loss. Secondary syphilis in 1917, and asymptomatic neurosyphilis in 1934, had apparently received adequate antiluetic therapy. He was referred for this study following subsidence of his last attack of jaundice. On examination he was moderately hypertensive (blood pressure 164 systolic and 100 diastolic) and obese. The skin showed numerous small scattered telangiectases, but no spider nevi. The liver was palpable 4 cm. below the costal margin and tender, but reverted to 1 cm. under further observation; the spleen was not enlarged. The gallbladder dye study was negative. Esophageal varices were not found. Increased capillary fragility was controlled by rutin. The blood sedimentation rate was persistently elevated, and the liver function tests impaired. These latter improved under observation for a number of months, and when stabilized, cytochrome c and sodium succinate were added to the usual regimen of high protein diet, multivitamins, brewers' yeast, and methionine. Fever and intense inflammatory induration resulted from the cytochrome c injections, which were discontinued after eight days, a total of 0.8 Gm. having been given. The patient was found to be hypersensitive to horse serum. (Our cytochrome c preparation was of equine origin).

The liver biopsies revealed considerable lymphocytic infiltration of the periportal areas, with little fibrosis, some prominence of the Kupffer cells and parenchymal degenerative changes, with moderate bile duct proliferation and occasional bile duct plugging. These were interpreted as indicating chronic infectious hepatitis in a pre-cirrhotic stage. Some regeneration was evident prior to the use of cytochrome c and sodium succinate, but was considerably increased subsequent to this therapy, as indicated by greater frequency of double nucleated cells, the appearance of triple nucleated cells, and increased variability in size of parenchymal cell nuclei.

Case 5. A 51 year old married negro male laborer had been an alcoholic since an early age. He lived on one meal a day, plus large amounts of whiskey, beer, and wine. For two years prior to hospital admission in September 1948, he had had anorexia and abdominal discomfort. In January 1948 he had been hospitalized for pneumonia and delirium tremens. He complained of cramping pain in the extremities on exercise, and of nervousness, restlessness, tremulousness, and irritability. Weight loss of 15 to 20 pounds had occurred in the past year.

He was fairly well developed and nourished, and did not appear ill, but was tense, anxious and tremulous. There was moderate edema of the lower legs and tremor and slight reddening of the tongue, with smoothing of its edges. The abdomen was moderately protuberant, and the liver was palpable 4 cm. above the iliac crest on the right, extending diagonally upward to the left rib margin, firm and not tender. The spleen was not palpable, but roentgen visualization (4) revealed moderate enlargement. The knees were enlarged (hypertrophic arthritis) and the skeletal muscles were hyperirritable. There were no sensory changes.

Therapy consisted of rest, high protein, low salt diet, with vitamin supplements, methionine, choline and brewers' yeast. The symptoms improved, but edema persisted, as well as moderate hypochromic anemia, elevated sedimentation rate, and occasional increased urinary urobilinogen. Febrile reactions occurred to two blood transfusions, and no more were attempted. No esophageal varices were found, and there was no history of hematemesis, but the patient was subject to epistaxis. Bleeding, clotting and clot retraction times, platelet count and capillary fragility were normal. Prothrombin times and liver function tests are recorded in Table I. The arterio-venous oxygen difference was normal.

Cytochrome c and sodium succinate were added from December 4 to March 22, the latter being continued further until discharge from observation. The liver edge was measured in the midclavicular line, and was 12 cm. from the costal margin in November and early December. By December 20, the measurement was 10 cm., on January 11, 8 cm., and on April 4, 5 cm.

The liver biopsies showed characteristic periportal cirrhosis of the Laennec type, with distorted lobular architecture, periportal fibrosis containing lymphocytic and some polymorphonuclear cell infiltration, bile duct proliferation, prominence of Kupffer cells, and, in the earlier biopsies, considerable degenerative changes in the parenchymal cells. Little regeneration was evident prior to enzyme therapy, but was marked subsequently, with numerous double nucleated cells, occasional cells with three and four nuclei, and marked variation in size and staining of the parenchymal cell nuclei. (Fig. 2, a and b). Increased regeneration was maximal March 1, but persisted through the last biopsy taken May 31.

Case 6. A 49 year old married white male committed patient had been a known general paretic for 12 years, and had been constantly hospitalized since 1946 for depressive and paranoid psychosis. He had had malarial fever and penicillin therapy. In 1947 he was found to have ankle edema, enlarged liver, spider nevi, reversed albumin-globulin ratio, and considerable impairment of liver function on laboratory testing. High protein, low salt diet, with multivitamins and brewers' yeast, considerably improved his laboratory findings

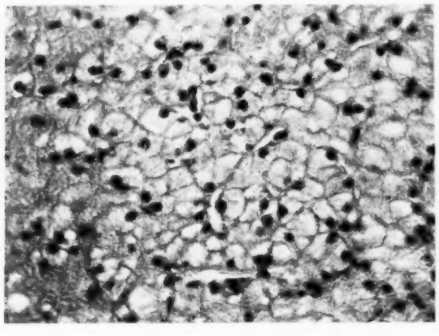

Fig. 2a. Areas of parenchymal cells from liver biopsies, case 5. Nov. 15, following stabilization on a hepatic regimen, and prior to enzyme therapy. H. and E., x240.

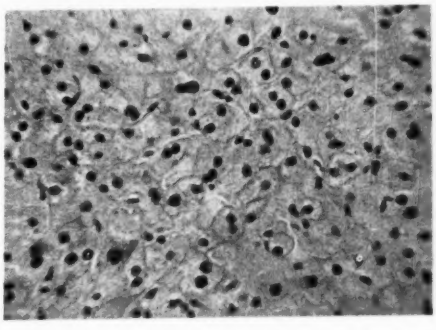

Fig. 2b. March 1, cytochrome c and sodium succinate administered since Dec. 4. Note increased variability of nuclei, with frequent double nucleated cells. H. and E., x240.

within a few months, and the edema subsided. He was referred for this study, and methionine added to his therapy in the interest of uniformity.

Liver biopsies showed periportal cirrhosis of the Laennec type, with marked fibrosis and complete loss of normal lobular architecture. The fibrotic tissue showed considerable lymphocytic infiltration, and bile duct proliferation. Hepatic cell damage was minimal, and there was evidence of regeneration in the form of double nucleated cells. These increased in number following cytochrome c and sodium succinate therapy, but not to a marked degree.

RESULTS

Clinical. Cases 1, 3 and 5 showed regression of liver and spleen size following cytochrome c and sodium succinate therapy, accompanied by improvement in symptomatology but little change in liver function tests. A similar effect was noted in our case of hepatolenticular degeneration treated with these respiratory enzymes. Whether this is a specific effect of such therapy is not known. The liver biopsies yielded no microscopic correlation with this change, other than increase in intralobular regenerating parenchymal cells, and, in case 3, disappearance of preexisting hepatic edema.

Liver function tests. Evaluation of the liver function tests (Table I) reveals no definite evidence of a trend toward improvement or impairment, in any case, nor in any specific test, which can be correlated with the administration of cytochrome c and sodium succinate, after maximal improvement had been obtained by the usual hepatic regimen.

Liver biopsies. All cases showed evidence of increased hepatic cell regeneration following cytochrome c and sodium succinate therapy, with maximal regeneration evident in the third month following initiation of such therapy, but continuing throughout the period of observation. It is to be noted that sodium succinate was continued as long as the patients were followed, while cytochrome c was administered for limited periods. Regeneration was marked in cases 1, 2, 4 and 5, and slight in cases 3 and 6. These two cases had the most severe degree of fibrosis of the series.

In none of the cases did regeneration approach the remarkable degree obtained in our earlier case of hepatolenticular degeneration. In that case, 11.2 Gm. of cytochrome c were administered over 127 days, three times the amount used in any of the cases in this series. The dosages of sodium succinate were more nearly comparable. In the present series, the degree of regeneration obtained could not be correlated with the quantity of cytochrome c administered.

DISCUSSION

The role of cytochrome ç and sodium succinate in tissue respiration is outlined in the report of our case of hepatolenticular degeneration (1). In that case, a valid theoretic indication for use of these enzymes in therapy was present in the form of a true tissue hypoxia, manifested by a reduced arterio-venous oxygen difference with normal rate of circulation. In the present series of cases, the enzymes were tried empirically, based on the observed hepatic regeneration of our original case, and on that found in rats by Drabkin (2). An arterio-venous oxygen difference and simultaneous circulation rate were determined at least once in each of the six cases of the experiment, and no evidence of tissue anoxia found.

There is no reason to suppose, therefore, that any deficiency in respiratory enzymes existed in these cases of chronic hepatic disease, nor would any be expected in Drabkin's partially hepatectomized animals. The effect observed may, perhaps, be attributable to increased tissue utilization of the enzymes. The low concentations of cytochrome c found in rapidly growing embryonic and malignant tissues as compared with mature normal tissues (5) is suggestive of a possible relation of this enzyme to growth processes, in addition to, or as a corollary of, its role in tissue respiration. Porphyrins other than cytochromes have been shown to have an accelerating effect on wound healing (6).

Other substances have been used in experimental attempts to induce hepatic parenchymal cell regeneration. Wilson and Leduc (7) obtained an increase in mitosis in mice using boiled and autolyzed liver, pulped kidney, and boiled egg yolk, in intraperitoneal injection. Their report reviews the literature of earlier attempts, using various liver fractions and trypan blue. These authors concluded that some specific chemical fraction of injured hepatic cells may be responsible for growth stimulation, and that other agents may operate through liver injury or overwork.

The natural stimulus to hepatic parenchymal cell regeneration is probably functional need (8). Liver tissue regenerates with extreme rapidity, total restoration after removal of two-thirds of the organ occurring within 10 to 14 days in adult rats on a high protein diet (2). Such regeneration is dependent upon the presence of an adequate vascular supply, being inhibited by constriction of the portal vein or diversion of the portal blood flow (9). It is impaired, also, by biliary retention (10). A high protein diet (11), and freshly cooked or powdered liver by mouth, but not crude liver extract (12), result in more rapid liver regeneration following partial hepatectomy. The thyroid exercises a regulating influence on rat liver regeneration (13).

Cases 3 and 6, which showed the least degree of parenchymal cell regeneration of this series, also had the greatest degree of fibrosis, and therefore probably the greatest interference with vascular supply to the parenchyma. In case 3, there was marked dissociation of parenchymal cells, all biopsies consisting of fibrous tissue containing isolated small nests of hepatic cells, with complete loss of lobular architecture. In case 6, there was marked fibrosis, with complete encirclement of numerous small hyperplastic nodules of parenchyma. That biopsies provide a reliable estimate of the degree of fibrosis of a cirrhotic liver is suggested by the study of Warren and Wahi (14), who found a high correlation between the amount of fibrous tissue microscopically visible in representative sections and that determined by weight of the digested whole organ. Case 3, in addition to the extreme fibrosis, showed marked biliary plugging and retention.

The shrinking of liver and spleen size which was observed following the enzyme therapy in cases 1, 3 and 5, as well as in the case of hepatolenticular degeneration previously reported, was not due to removal of fat infiltration, according to the biopsy evidence. The use of lipotropic agents in the period of preparatory therapy had accomplished that in all the cases. Nor was there any evidence that necrotic processes were involved, either clinically or in the biopsies.

There was no progressive increase in fibrosis. Case 3 did show disappearance of hepatic edema previously present. We are led to conclude that the change was largely a result of shift in blood storage by these organs. The normal adult human liver has been estimated to accommodate without distention over 800 cc. of fluid. Its blood storage may be varied by phases of activity and inactivity of the sinusoids and capillaries, by filling and emptying of small endothelial tubes situated within the walls of the sublobular and central veins and guarded by valve-like sphincters, by opening or closure of sphincters at the exits of the sinusoids, by the tone of the sphincter mechanism guarding the entrance of the hepatic veins into the inferior vena cava, and by lymphatic drainage. These influences on liver blood volume are reflected in the vascular content of the spleen and the intestinal tract, which drains into the portal system. The entire hepatic and portal vasculature may hold as much as 55% of the total blood volume (15). The manner in which cytochrome c and sodium succinate may have influenced this storage system remains unexplained.

CONCLUSION

In view of the lack of improvement in liver function tests, and the debatable influence on the clinical course of these cases, the use of cytochrome c and sodium succinate in chronic hepatic disease can hardly be recommended on the basis of this limited experience, despite the histologic evidence of increased regeneration of parenchymal cells obtained.

SUMMARY

The addition of parenteral cytochrome c and oral sodium succinate to a standard regime of therapy in six cases of chronic hepatic disease resulted in histologic evidence of increased hepatic parenchymal cell regeneration. Liver function remained unaltered as measured by standard laboratory procedures. In three cases, shrinking of liver and spleen size occurred, attributed to vascular factors.

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THE TAKATA-ARA REACTION IN THE DIFFERENTIAL DIAGNOSIS AND PROGNOSIS OF JAUNDICE

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INTRODUCTION

THE Takata-Ara Reaction (TAR) was first used as a liver function test by Jezler in 1929 (1). In a 1940 review of experiences with this test (2) it was concluded that there is considerable difference of opinion as to its value in the diagnosis of liver disease and that its basis is obscure. The value of the TAR alone in the differential diagnosis of jaundice, or in combination with other tests has been pointed out by several authors (3,4,5,6,7) while others have also attributed to it some prognostic value. (2,8) A number of workers have considered the test of value only in indicating liver damage and useless or of little significance in differential diagnosis. (2,9,10)

In the study of a large number of jaundiced patients the TAR proved itself of differential diagnostic aid. Hence, an attempt was made to re-evaluate the differential diagnostic significance of the TAR on the basis of recent classification of hepatobiliary diseases.

The TAR has been considered by some as a simple function of the albumin-globulin ratio. (11,12,13,14) Others have considered it not merely a simple response to an increase in globulin and/or fibrinogen or a decrease in albumin but also an expression of other factors, such as, either (a) a deficiency in some protein which ordinarily prevents the action (protective colloid effect) (6) or (b) the presence of a special sub-

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stance which precipitates easily with the mercuric ion (6,15,16,17,18,19).

Still others postulated the presence of "Takata proteins" which, on salting out, fell into the euglobulin and fibrinogen globulin fractions and wandered with the gamma and perhaps the beta globulins. (15) These "Takata proteins" were considered a substance not normally present in blood. This view was supported by others (5,20,) who showed that the TAR depended on an increase of the "globular proteins," similar to the euglobulins and pseudoglobulins I. They assumed that pathologic changes occurred in these proteins, altering their colloid properties so that they resembled fibrinogen. Some observers (17,18,19) found that a positive TAR could be produced by adding the sulfur containing amino acids, the diamino acids and diamines to serum and that the resulting precipitate was in part mercuric oxide and in part the mercuric salt of the protein. In TAR positive sera they also found an increase in tryptophane, but a decrease in cystine. (19) This last finding agrees with Haarman's observation that in alkaline solution the mercuric ion forms a firm combination with the protein molecule and that this combination seems to depend on the NHCO group of the protein molecule, the nitrogen atom of the imadazole nucleus (an important part of the tryptophane molecule) and the sulfur atom of the cystine molecule. (21) In general, however, no correlation was established between the amino acid content of the serum and the result of the TAR.

MATERIAL AND METHODS

The TAR was performed 356 times on 264 patients as part of a series of tests which included the cephalin-cholesterol flocculation (22), thymol turbidity (23), zinc sulfate turbidity (24), and determination of the albumin-globulin ratio and total serum bilirubin. One hundred and ninety-five series of tests were done on 178 patients who had active hepatitis or cirrhosis; 75 series of tests on 22 of the 178 cases, while they were in the recovery phase of hepatitis or in the inactive stage of cirrhosis. One series of tests each was done on 86 patients with obstructive jaundice.

The study was conducted in two ways: (1) the TAR was compared with the other flocculation tests in the differential diagnosis of jaundice, and (2) the test was correlated with the changes in clinical status, biopsy findings and changes in the other liver function tests. The latter was done on a group consisting of 40 patients upon whom 115 series of tests were performed. Twenty-three of these patients had 2 series of tests, 17 had 3 or more series embracing periods of time from one week to one year.

Readings of 3+ and 4+ in the TAR were considered positive. The test was performed according to the method of Wayburn and Cherry (4).

RESULTS

The TAR was positive in a high percentage of cases of postnecrotic and Laennec's cirrhosis but only in a comparatively small percentage of cases of acute hepatitis (except in homologous serum hepatitis) and in a still smaller percentage of patients with obstructive jaundice. In fatty cirrhosis the percentage of positive TAR's was lower than in the more advanced stages of cirrhosis. Homologous serum hepatitis (HSH) showed a marked difference from the infectious variety of viral hepatitis in the percentage of positive TAR's (Table 1). The percentage of positive TAR's in toxic hepatitis was intermediate between infectious hepatitis and HSH. In obstructive jaundice the percentage of positive TAR's was relatively low. Malignancy with complete obstruction gave a higher percentage of positive TAR's than benign, incomplete obstruction, which had the lowest percentage of positive results; this latter observation held true also for the other flocculation tests.

The percentage of abnormal results in the other flocculation tests (other than the TAR) was correspondingly high for postnecrotic and Laennec's cirrhosis. (7) Fatty cirrhosis showed a considerably lower percentage of abnormal results in all flocculation tests. In obstructive jaundice all the flocculation tests including the TAR and A/G ratio were rarely positive unless sepsis coexisted.

In a high percentage of cases with infectious hepatitis all the flocculation tests except the TAR and the

TABLE I. PERCENTAGE OF POSITIVE RESULTS IN A SERIES OF FLOCCULATION TEST IN PATIENTS WITH VARIOUS TYPES OF JAUNDICE

Diagnosis	No. of Tests	TAR Positive (3+-4+)	Zinc Sulfate Turbidity Positive (more than 12.5 U)	Cephalin Positive (2+-4+)	Thymol Turbidity Positive (more than 5.0 U)	A/G Ratio less than 1.2
Cirrhosis	115	82.3	92.9	79.6	79.6	67.3
(1) Laennec's	90	87.8	96.7	83.3	81.1	72.2
(2) Fatty	14	35.7	64.3	42.9	64.3	35.7
(3) Postnecrotic	9	100.0	100.0	100.0	100.0	66.7
Hepatitis	82	34.1	78.0	78.0	80.5	25.6
(1) Infectious	28	10.7	91.3	92.8	85.7	14.3
(2) HSH	25	66.7	92.0	80.0	96.0	44.0
(3) Toxic	29	27.5	55.2	62.1	62.1	20.7
Obstructive Jaundice	86	9.3	17.4	22.1	58.8	17.6
(1) benign and/or incomplete	51	2.0	9.8	2.0	19.6	4.0
(2) malignant* and/or complete	35*	20.0	28.6	20.0	48.6	20.0

*Including cases of purulent hepatitis.

TABLE II. MEAN VALUE OF THE OTHER FLOCCULATION TESTS IN CASES WITH POSITIVE CEPHALIN-CHOLESTEROL TESTS

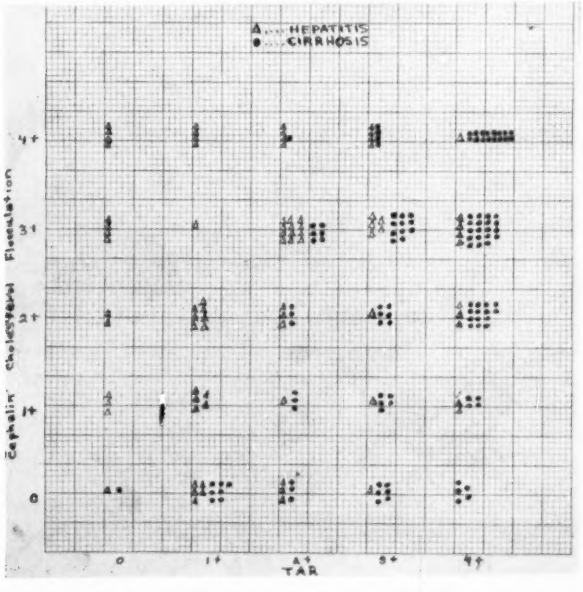
Diagnosis	No. Cases	TAR	Thymol Turbidity	Zinc Sulfate Turbidity
Laennec's Cirrhosis	70	3.4+	9.0	27.8
Fatty Cirrhosis	5	2.6+	8.7	21.1
Postnecrotic Cirrhosis	9	3.6+	14.0	34.0
Infectious Hepatitis	25	1.6+	13.1	19.6
Homologous Serum Hepatitis	18	3.0+	13.7	25.4
Toxic Hepatitis	18	2.2+	9.5	14.3

albumin-globulin ratio were pathologic. In HSH however, the TAR and albumin-globulin ratio were also abnormal in a high percentage of cases. In patients with toxic hepatitis all flocculation tests were less frequently abnormal while the TAR and albumin-globulin ratio were positive in a relatively higher percentage of cases.

No parallelism was found between the TAR and the cephalin-cholesterol flocculation or the thymol turbidity tests. (Graphs 1 and 2). Many cirrhotics with positive TAR's had negative cephalin-flocculation tests and conversely many more patients with hepatitis with positive cephalin-flocculation tests had negative TAR's. The same was true for the thymol turbidity test. In

TABLE III. MEAN VALUE OF THE OTHER FLOCCULATION TESTS IN CASES WITH A NEGATIVE CEPHALIN-CHOLESTEROL TEST

Diagnosis	No. Cases	TAR Positive	Thymol Turbidity Units	Zinc Sulfate Turbidity Units
Laennec's Cirrhosis	20	3.0+	4.9	21.7
Fatty Cirrhosis	9	1.3+	4.2	15.0
Postnecrotic Cirrhosis	none	—	—	—
Infectious Hepatitis	3	0.3+	7.3	12.7
Homologous Serum Hepatitis	7	2.4+	7.8	17.5
Toxic Hepatitis	10	1.1+	5.3	12.8



Graph 1: Distribution graph showing lack of relationship between the TAR and the cephalin-cholesterol flocculation.

approximately 40 percent of the cases in graphs 1 and 2 there was a lack of correlation between the respective tests.

On the other hand, a moderate parallelism was found between the TAR and both the zinc sulfate turbidity and albumin-globulin ratio, (Tables II and III, graphs 3 and 4).

When those cases of hepatitis and cirrhosis which had a positive cephalin-flocculation are selected, the determination of mean values for the other flocculation tests shows no parallelism between the TAR and the thymol turbidity and moderate parallelism between the TAR and the zinc sulfate turbidity except in infectious hepatitis where the latter is moderately elevated while the TAR is negative. This exception is less marked in toxic hepatitis and not present in HSH.

There is no parallelism between the TAR and the total serum bilirubin or the duration of jaundice. In a comparison of HSH with the infectious variety of viral hepatitis it is seen that a fair percent of cases of HSH with a positive TAR have a much lower total serum bilirubin than cases of infectious hepatitis having a negative TAR (graph 5).

Distribution curve patterns for the TAR, thymol turbidity and zinc sulfate turbidity in cirrhosis and hepatitis show that the TAR and the zinc sulfate turbidity test have a pattern which is parallel, and is different from the pattern of the thymol turbidity test. The cephalin-cholesterol flocculation distribution curve does not show such a distinctive pattern since it is not a strictly quantitative test and is positive in a high percentage of both diseases.

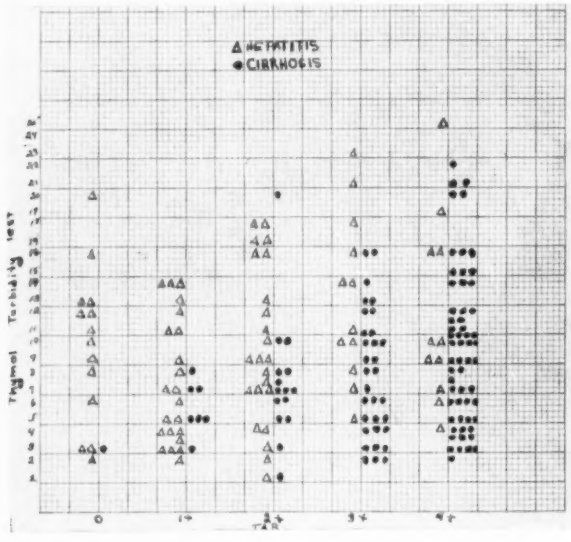
In a critical review of the results of 115 series of tests done on the 40 patients in various phases of hepatitis, or cirrhosis, the TAR was found parallel to the zinc sulfate turbidity but not parallel to the cephalin-cholesterol flocculation or thymol turbidity in the great majority of cases.

In 4 cases of hepatitis which progressed to cirrhosis, the TAR either remained elevated or became positive. A positive TAR was found only once in another group of 4 cases of chronic hepatitis which had not progressed yet to cirrhosis, although the TAR was rising (not yet in positive range) in another 2 of them. In two cases of fatty cirrhosis going over to the non-fatty type the TAR also became positive. These latter cases were followed by serial biopsies.

DISCUSSION

Of the various flocculation tests used to distinguish the different types of jaundice the TAR has been considered among those with the least apparent basis. Its seeming lack of specificity (it is sometimes positive in the presence of febrile diseases, such as, pneumonia or tuberculosis and negative in the presence of proved alteration of the liver), and the difficulty of obtaining reproduceable results have kept it from being a widely used test.

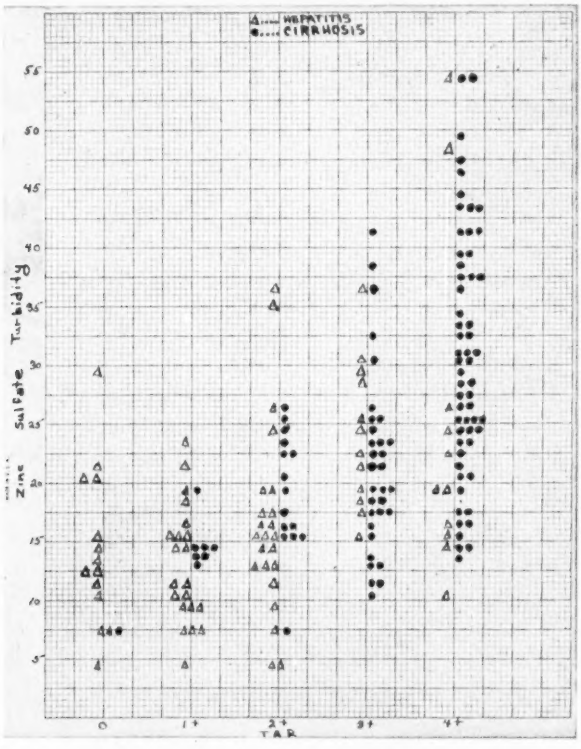
In our patients with icterus, however, the TAR (when used as one of a series of flocculation tests) has been of particular value in differentiating the various types of hepatitis from cirrhosis, (7) and in the non-icteric cases it has helped in the differentiation of patients with cirrhosis from those with enlarged non-cirrhotic livers.



Graph 2: Distribution graph showing lack of relationship between TAR and the thymol turbidity test.

The fact that most cases of fully developed cirrhosis have a positive TAR is helpful in the diagnosis of icteric patients in whom the other flocculation tests may be equivocal. Cases with a combination of positive TAR, very high zinc sulfate turbidity, low thymol turbidity and variable cephalin flocculation usually proved to be Laennec's cirrhosis, while those with positive TAR's, high zinc sulfate turbidity, high thymol turbidity and positive cephalin flocculation turned out to be HSH or post-necrotic cirrhosis. Since it may not be easy to decide at which level a thymol turbidity elevation can be considered marked or slight we have ly. Advanced cases of passive congestion of the liver may show a positive TAR (cardiac cirrhosis). Large, fatty livers without a cirrhotic component were not found to have a positive TAR. A patient with severe jaundice or liver damage (as shown by other flocculation tests) and a negative TAR will almost never be a cirrhotic.

The TAR is not only of help in the diagnosis of cirrhosis but also pointing out the homologous serum variety of viral hepatitis, which, in recent years, has become an increasingly important problem. A differentiation of HSH from the infectious variety of viral



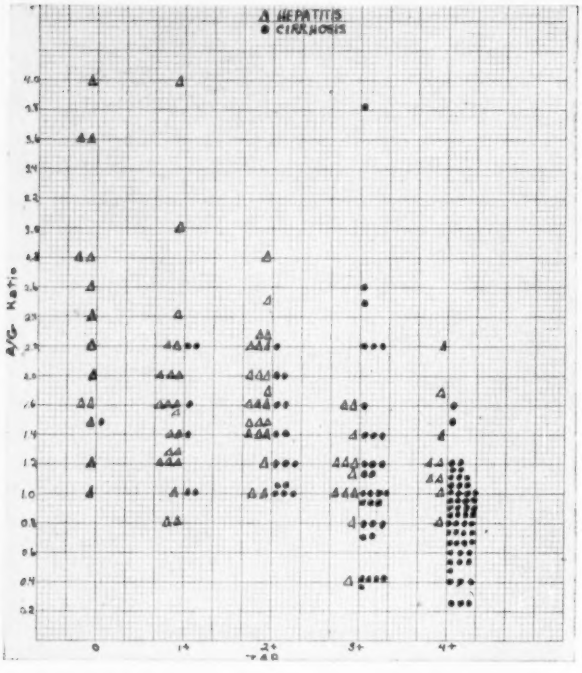
Graph 3: Distribution graph showing moderate relationship between the TAR and zinc sulfate turbidity.

attempted to use the zinc sulfate turbidity, thymol turbidity ratio as an indicator of cirrhosis. In cirrhosis this ratio is usually three or more while in hepatitis it is seldom more than two. Cases of cirrhosis with negative TAR's are usually in a recovering phase. It should be pointed out, however, that during severe hematemesis the TAR may become negative. (25) In our series two such instances were encountered, but the basis for this is as yet unknown.

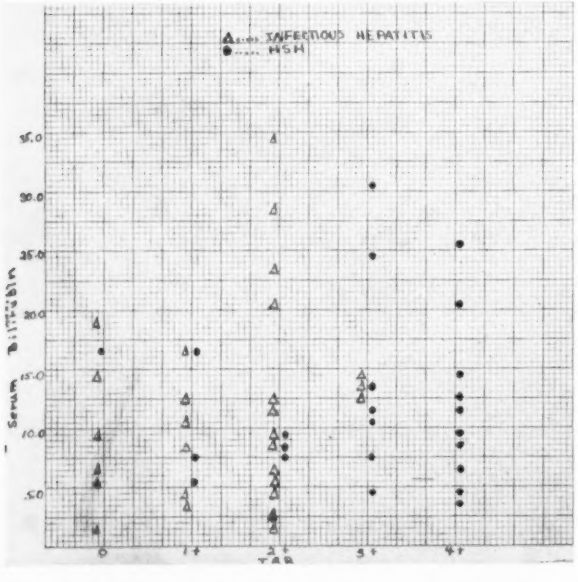
The high incidence of positive TAR's in cirrhosis without jaundice is a helpful factor in distinguishing cirrhosis from other non-icteric forms of hepatomega-

hepatitis is at times of more than academic interest (26). In the infectious variety of viral hepatitis the flocculation tests, including the zinc sulfate turbidity, were positive in a high percentage of cases, while the TAR was negative. HSH, however, had a positive TAR and a high zinc sulfate turbidity in about 60 per cent of the cases, even when the clinical course, as measured by the degree of jaundice, was not of great severity.

It appears, therefore, that in HSH the TAR is not merely an index of the severity of hepatitis; but that it indicates some different, as yet unknown, but sig-



Graph 4: Distribution graph showing moderate parallelism between TAR and A/G ratio.



Graph 5: Shows lack of parallelism between TAR and total serum bilirubin in infectious hepatitis and HSH.

nificant change in the plasma proteins which is not present in the infectious variety of viral hepatitis. The changes may be simply quantitative and/or qualitative due to the presence of the "Takata proteins" or some other protein components (*27*).

The existence of a positive TAR in some cases of toxic hepatitis is not surprising. Some of our cases of toxic hepatitis were secondary to diseases, such as, pneumonia which per se have changes in the serum proteins. The TAR is negative in cases of obstructive jaundice; whenever it becomes positive the other flocculation tests are also positive.

Prognostically, a rising TAR or persisting TAR in a case of hepatitis points to chronicity with change into cirrhosis. The test can thus be used for the evaluation of (a) a patient's progress and (b) the results of therapeutic procedures.

Purely technical matters may account for the discrepancy in the results of the TAR obtained by various observers. It is definitely established that the TAR is more often positive in plasma than in Serum (28), and at lower temperatures than at higher ones (29), in febrile conditions than in non-febrile states (25). All these factors must be considered in the evaluation of the results of the TAR.

SUMMARY

An attempt was made to re-evaluate the TAR on the basis of 264 patients suffering from various types of jaundice. Although it is recognized that mere technical difficulties in the reproduction of the reaction may interfere with the interpretation of the results, in some well-defined circumstances the results of the TAR may be of crucial import in the differential diagnosis of jaundice, especially when the other flocculation tests are equivocal. These conditions are: differentiation of acute hepatitis from cirrhosis, recognition of the transition of hepatitis into cirrhosis and possibly also differentiation of the homologous serum variety from the infectious variety of viral hepatitis.

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PSEUDOAGGLUTINATIVE EFFECT OF EQUINE GASTRIC MUCIN ON HUMAN ERYTHROCYTES AND SUGGESTIVE EVIDENCE OF AN ANTI-Hr COMPONENT THEREIN

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A PSEUDOAGGLUTINATIVE effect whereby certain muco-proteins caused clumping of suspensions of human erythrocytes, has previously been reported (1, 2,3). In the instances of hog gastric and parotid mucins, this pseudoagglutinative effect seemed to parallel the Rh positivity of the erythrocyte samples. Further studies in which hog mucins were separated by fractional ammonium sulfate precipitation, indicated the extreme heterogeneity of the pseudoagglutinins so that such parallelism is tenuous except to the individual who actually performs the comparative tests. Nevertheless, it appears to hold to a significant degree.

A recent examination of horse gastric mucin has revealed for it, a comparable heterogeneity of pseudoagglutinative effect but without any tendency of parallelism to Rh positivity. In fact the initial tests gave the impression of a reverse trend. Certain theoretic considerations mandated a closer examination of this trend.

That Rh negative erythrocytes could be antigenic and could cause sensitization of Rh positive human subjects, was a theoretic consideration derived by Levine (5). He reported an instance of such sensitization and designated the antigenic factor as Hr. Hr blood types are "reciprocal" to Rh and are consequently Rh "negative" in their reciprocal category. Instances of Hr sensitization are exceedingly uncommon; their rarity probably reflecting a relatively low antigenicity. In determining hetero-or homozygeity of Rh positive subjects, Hr antiserums find some application. Their dearth poses a difficulty in this regard and attempts have been made to sensitize human volunteers. Pur-

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posive human sensitization for the preparation of any serum has the drawback that many physicians are reluctant to admit the propriety of such active immunization since blood is a complex antigen and remote effects can not always be predicted. If it were possible to designate human blood types on the basis of their reaction to (presumably) reduplicable animal anti-serums, some advantage might be forthcoming.

It is for this reason that our preliminary results with crude horse gastric mucin are presented.

Horse gastric mucin* was dissolved in physiologic saline to concentrations varying from ½ to 5%. In some instances, bovine albumin fortification was used but later abandoned when it was found that the mucins themselves imparted a sufficiently high dielectric constant to their solutions. The slide test of Diamond (6) was adapted to a five minute exposure of the erythrocyte suspension in citrated plasma as in the porcine fraction studies (3). In this case, however, agitation of the mixtures was effected by placing the ringed slides on a rotator used for the Mazzini serologic test. Because of the constancy of the experimental conditions, pseudoagglutination was designated in an eight degree range (very, very strong, very strong, strong, positive, weak, very weak, very, very weak, and negative) instead of in the "number of pluses" used in the first report (2).

*Supplied by the Medical Research Division of Sharp and Dohme of whom the authors wish to thank Dr. Louis A. Kazal.

RESULTS

These are shown in Table I which records the Rh phenotypes, Hr designation and the effects of various concentrations of equine gastric mucin on various human blood samples. The specific hemagglutination types (A, B, AB and O) are not in every instance recorded since in that connection, there was absolutely no correlation. This absence of correlation appears at first glance to obtain for Rh and Hr until the quantitative aspects are examined. Then it is found that there is a trend toward stronger agglutination of Hr positive than of the Hr negative samples. This trend obtains in spite of the fact that certain Rh negative bloods (which must be Hr positive) are negative to equine

TABLE I

Number	Type	Human Rh	Agglutination by Human Hr	Horse Gastric Mucin 3%	2%	1%	½% in bovine albumin
1708	AB	$Rh_{2,2}$	Pos	Ps	P	Pvw	N
1709	O	Rh_1	Pos	Pvs	Ps	P	Pw
1710	O	rh		Pvs	P	Pvw	Pw
1711	A	Rh_2	Pos	Ps	P	Pw	N
1712	O	Rh_1	Pos	Ps	P	Pw	N
1717	A	Rh_1	Neg	Ps	P	N	N
1720		rh		Pw	N	N	N
1721	B	Rh_0	Neg	P	Pw	Pvvw	N
1740	O	$Rh_{1,2}$	Pos	Ps	P	Pw	N
1741	A	Rh_1	Pos	Pvs	Ps	P	Pvw
1742	O	Rh_1	Neg	Pw	Pvvw	N	N
1743	O	rh		Pvvs	Pvs	Ps	Pw
1744	A	rh		Pvs	Pvs	Ps	Pw
1745	A	$Rh_{1,2}$	Pos	Pvs	Pvs	Ps	Pw
1746	A	Rh_2	Neg	Pvs	P	Pw	Pvw
1747	O	rh		Pvvs	Pvs	Ps	P
1748	B	$Rh_{1,2}$	Pos	Pvs	Ps	Pw	Pvvw
1749	O	$Rh_{1,2}$	Pos	Pvs	Ps	P	Pvw
1750	O	Rh_1	Neg	Pw	Pvvw	N	N
1751	B	Rh_1	Pos	Ps	P	N	N
1752	O	rh		Pvs	Pw	Pw	N
1762	O	Rh_1	Neg	Ps	Pw	Pvvw	
1763	O	Rh_1	Pos	Ps	P	Pw	
1767	A	rh		Ps	Ps	P	
1770	B	rh		P	P	Pvw	
1771	O	rh		P	P	Pw	
1772	O	rh		Ps	Ps	Pw	
1773	A	Rh_1	Neg	Pw	N	N	
1775	A	Rh_1	Neg	Pvs	Ps	P	
1776	O	Rh_1	Neg	Pvs	Ps	P	
1777	O	Rh_2	Pos	Ps	Ps	P	
1780	A	$Rh_{1,2}$	Pos	Ps	P	Pw	
1782	A	$Rh_{1,2}$	Pos	P	Pw	Pvw	
1790	AB	rh		Pvvs	Pvvs	Pvs	
1791	AB	rh		Pvvs	Pvvs	Ps	
1792	B	rh		Pvvs	Pvs	Ps	
1793		rh		Pvs	Ps	P	
1794		Rh_2	Pos	Pvs	Ps	P	
1795	A	rh		Ps	P	P	
1796	A	$Rh_{1,2}$	Pos	P	Pvw	N	
1797	O	Rh_1	Pos	Pvs	Ps	P	

mucin while certain Hr negative bloods are equine positive throughout the range of mucin concentrations. A correlation is even more suggestive when the rate (avidity) of agglutination between Hr negative and positive bloods is observed, though in the case of pseudoagglutination (as here) rates do not lend themselves to tabular designation.

DISCUSSION

As in the case of porcine mucin pseudoagglutination, we appear to be dealing with heterogeneity of effect, some component of which is probably the "non-specific" mucoprotein effect (3); in higher mucin concentrations only an occasional erythrocyte sample fails to show pseudoagglutination. Discordancy between human anti-Hr serum and equine mucin in the weaker dilutions of the latter may find explanation on the basis of either two premises (1) that any resemblance to true anti-Hr activity of horse gastric mucin is coincidental or (2) that the correlation exists but is rendered less perceptible by the masking effect of non-specific mucoprotein. This would appear to be negated by those instances in which Hr positive erythrocytes are negative throughout the horse mucin concentration range. However this mucin preparation contains appreciable amounts of "B" substance (which masks "B" agglutination); it may likewise contain substances which act as haptenes toward certain subgroups of Hr.

The last premise is an interesting one. The known association of "A" substance with hog gastric mucosa which also apparently contains an anti-Rh pseudoagglutinin (2) again directs attention to a recent implication (7) of a possible antigenic connection between group B and the Hr factor. The connection was only elicited (and then very indirectly implied) on the basis of quite extensive statistical analysis. Any true association of the "B" substance in horse gastric mucin with anti-Hr could only be conclusively demonstrated by the same type of analysis. Because of the theoretic and practical importance of such a connection, an analysis of the results with various equine mucin fractions is now under way.

Perhaps some apologies are in order for bringing an apparently abstruse and as yet unestablished set of problematic genetic relationships to the attention of the practicing gastro-enterologist. The attempt however is more than just well intended. There are two sets of reasons, one practical and the other academic as to why gastro-enterologists must become more directly concerned with the present inadequacies of blood transfusion practice and the (as yet) uncircumventable problems that arise in its connection.

In the first case, gastro-enterologic situations form a major indication for blood transfusion and otherwise salvagable lives have been lost because these indications have not properly been met. In our own experience in a large general hospital, the gastro-enterologic service (medical and surgical units) gave, in numbers of instances and total quantity, an amount of blood second only to that of the obstetrical-gynecologic service. The reasons for this large utility are at once apparent. Bleeding gastric ulcer requires multiple transfusions for either its operative or non-operative management and we have advocated massive, repetitive transfusions in the palliative treatment of non-operable gastric carcinoma (8). In the long drawn out course of gastric resections or gastrectomies, call is made frequently for transfusion while the patient is under deep general anesthesia. Here the transfusionist is figuratively walking an "ordeal by blood" for there are no overt manifestations of an incompatability reaction and we have likewise directed attention to the apparent frequency of unexplained agglutinins in such cases (2).

Perhaps the origin of the latter will only find explanation when there has been adequate exploration of what is behind the *fact* that there is a rather remarkable association of "blood group" factors with the alimentary canals, not only of humans but of other mammals as well. Up to the present set of reports, those concerned were the classic A and B substances, the first usually associated with the hog and the second, with horse stomach. Ascaris suum, an intestinal canal inhabitant, has both A and B agglutinogens (9) and one indeed wonders about the purposiveness of their presence. These materials are referred to and probably with some justification as "group-specific" substances but specificity is a looser term biologically than etymologically. Kazal and his associates have found A as well as B substances in large amounts in the tissues of some horses; not only in the gastric mucosa but also in the saliva. Curiously enough, a horse might be of one "type" insofar as the saliva was concerned and of an entirely opposite, or a mixture of types with respect to its gastric mucin (10). Schiff and Weiler (11) have found a remarkable "blood group enzyme" in both saliva and feces on whose physiologic significance and pathologic consequence, DeBarondes and Kane (12) have made some pertinent comments. All of the foregoing substances *prevent* erythrocyte agglutination. That which we describe and which likewise apparently is intimately associated in some as yet unknown manner with alimentary tract function, is an active agglutinator of human erythrocytes. Perhaps their implication, pathologically, would be much more serious were this function to be deranged. This is not known; it is being posed as a question of concern to the gastro-enterologist.

A final point on the problematic significance of these pseudoagglutinins, is bound to be in order not only to gastro-enterologists, but to any physician. The point emerges as a series of pointed questions. How "specific" are the "blood group-specific" substances in either their antigenic or antibody phases? What specificity can be attributed to mucoproteins that show certain similarities to the Rhesus factor and how specific are these factors which they mimic. How secure is the geneticist and the serologist in submitting his statistical tables to prove or disprove paternity and how much credence should be placed by those who adjudicate.

The laboratory serologist, hematologist, immunologist and biostatistician may well be within his rights and time may prove his present contention. But progress dictates that this proof be strengthened by the heckling of those physicians who can recall how "specific" were once regarded the so-called "serologic tests for syphilis, how the serologist impressed their infallibility upon courts of law and legislative bodies in face of the few feeble voices that were reminding those who should have known better that the "specific" antigen used in this "specific" test for this "specific" disease, was a lipoid extractable from normal cow heart (13). How sheepishly we are meeting the pay-off in this connection mandates that, correct or otherwise in the final analysis, we continue to explore the properties of mucoid pseudoagglutinins.

SUMMARY

Horse gastric mucin differentially pseudoagglutinates human erythrocyte suspensions. Suggestions of a selective trend toward pseudoagglutination of Hr positive samples is noticed.

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Addendum: The non-specific role of mucins in erythrocytic pseudoagglutination has been demonstrated by the recent elicitation of this phenomenon with an artificial mucinoid, sodium carboxymethyl cellulose.

FIFTEEN YEARS' STUDY OF OCCULT LYMPHOCYTOSIS IN 280 HYPERCHOLESTEROLEMIA PATIENTS

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TREATMENT and study over a fifteen year period of 280 hypercholesterolemia patients has disclosed a symptom triad including the following:

1. A relative lymphocytosis
2. Hypercholesterolemia
3. Hypothyroidism.

Various experimental investigations agree in establishing an inverse relation between the thyroid sluggishness and the blood levels of cholesterol.

For example, Artom (1), (2), reported the increase in blood cholesterol levels of thyroidectomized dogs. Perlzweig (3), observed a decrease in the total blood lipids of hyperthyroid cases. Knauer (4), reported a decrease in the blood lipids in hyperthyroidism and an increase in hypothyroidism.

Westra and Kunde (5), showed that the high blood cholesterol levels in certain rabbits could be reduced by feeding thyroid. Mason, Hunt and Hurxthal (6), found a decrease in blood cholesterol levels in hyperthyroidism which was generally lowest in proportion as acute toxemia prevailed. Gilligan and associates (7), demonstrated that blood cholesterol levels are related to the basal metabolic rate. Not all drugs that stimulate basal metabolism lower blood cholesterol levels. For example, Cutting, Rytand and Tainter (8), raised the basal metabolic rate by administering dinitrophenol. It lowers the respiratory quotient, which implies a selective oxidation of fat rather than an enhanced oxidation of all foodstuffs, but it does not lower blood cholesterol. Tuttle (9), reported that most of the patients having diabetes mellitus for a number of years showed disturbances of the vascular system to a varied degree, depending upon the length and control of the disease. Out of 88 cases, sixty-five or 73.8 per cent, showed hypercholesterolemia in this study of "Diabetes Mellitus. Factors Influencing Cause, Course, and Complications. Analysis of 88 Cases."

Joslin, Eliot (10), makes a similar prognosis, and strongly favors the belief that the usual increase in the cholesterol in the diabetic blood is responsible for the vascular change.

Tuttle (11), found hypercholesterolemia in almost all of 500 obesity patients treated. The rationale of treatment was based on the need for proteins to maintain cellular integrity. With weight loss, there was a progressive reduction in blood cholesterol.

Thyroid extract (1) raises the metabolic rate, (2) contributes to fat oxidation including (3) the lowering of blood cholesterol, and in addition, (4) it influences the maturation and differentiation of cellular elements.

OCCULT LYMPHOCYTOSIS

Differential white cell counts were made according to the method suggested by Arneth as described by Wintrobe (12).

The basis of the classification was the number of lobes of which the nucleus was composed. The lymphocytes were classed into large and small, the difference being, not so much one of actual diameter, but rather the relative proportion of cytoplasm to nucleus. Small lymphocytes appear as if their nucleus almost completely usurps the cell, there being a barely perceptible cytoplastic margin; whereas large lymphocytes show a wide margin of cytoplasm surrounding the nucleus. In size, the large lymphocytes are nearly always of much wider diameter than the small lmphocytes.

Typically illustrative of the findings are the counts, made as described in the following cases (Table 1).

Two conspicuous characteristics are notable. Of the multilobed white cells, the more "mature" forms tend to be increased. This would be a "shift to the right" by the Arneth or Schilling interpretation. It suggests an emphasis of the more matured forms of neutrophilic cells. The preponderance of mononucleated forms is even more characteristic. Frequently, the number of lymphocytes is in excess over the number of neutrophiles. In all cases, there is a relative lymphocytosis; and in some cases, there is an actual lymphocytosis despite the nearly normal total white cell count. For example, the average total normal white cell count is 7,000 cells per cubic millimeter of blood. Of this number, about 2,100 are normally lymphocytes (from 27% to 33% of the total white cells). When the lympho-

TABLE I

Case History Number		Arneth Classification of Polys					Mononuclear Cells			Total	Lymphocytic Index
		1	2	3	4	5	Polys	Small	Large		
11	C-1	9	26	43	19	3	50%	30	20	50	1.66
23	C-2	2	18	42	36	2	48	48	3	51	1.67
39	C-3	15	32	36	14	3	45	52	3	55	1.83
52	C-4	5	33	46	16	0	51	40	9	49	1.63
68	C-5	2	4	34	40	22	40	40	20	60	2.00
82	C-6	2	8	28	41	21	54	31	15	46	1.53
93	C-7	2	12	58	28	0	37	46	17	63	2.10
106	C-8	10	14	38	26	12	41	24	35	59	1.96
120	C-9	1	14	36	40	9	55	12	33	45	1.50
131	C-10	1	5	30	39	25	53	10	37	47	1.56
140	C-11	4	14	48	28	6	49	40	11	51	1.70
156	C-12	6	14	30	40	10	50	32	18	50	1.66
167	C-13	7	19	36	30	8	53	23	24	47	1.51
182	C-14	4	8	44	32	12	39	25	36	61	2.03
193	C-15	6	15	49	25	4	48	29	23	52	1.73
201	C-16	5	20	45	26	4	47	29	24	53	1.77
215	C-17	2	20	50	20	8	50	25	25	50	1.66
235	C-18	6	12	38	34	10	30	52	18	70	2.33
240	C-19	1	24	40	32	3	24	11	65	76	2.53
272	C-20	7	19	51	20	3	39	38	23	61	2.00
278	C-21	2	3	39	46	10	43	15	42	57	1.90

(For easy recognition of the degree of occult lymphocytosis, a "lymphocytic index" has been used in this study. It is obtained by dividing 30 (representing the average normal percent of lymphocytes) into the actual percent of lymphocytes found. For example, Case 39 shows 55% lymphocytes; therefore, 55/30 gives a lymphocytic index of 1.83).

cytes amount to over 50% of the total white cells, as is seen in many of the cases, the actual total lymphocytes per cm. of blood can be considerably higher than the normal 2,100 and may range from 2,500 to 5,000 or more.

We are dealing with an occult lymphocytosis. Hidden in the approximately normal total white cell count of the blood of the hypercholesterolemic patient with hypothyroidism is a real lymphocytosis. This is manifested as a relative lymphocytosis on differential count and expresses an increase above normal of lymphocytic cellular output.

All blood cells are derived from the mesenchyme. The parent hemoblast is actually a huge lymphocyte, from which both red and white cells are subsequently differentiated. This is related to bio-oxidation. Sabin (13), for example, has developed experimental evidence to show that leucocytic differentiation is related to oxygen tension.

Occult lymphocytosis in hypercholesterolemia with hypothyroidism indicates inadequate cellular differentiation. Therapeutic measures are directed to 1) diet, 2) thyroid stimulation, 3) weight control, 4) psychotherapy, 5) bio-oxidation, 6) lipotropic agents and 7) supportive measures.

TREATMENT

1) Diet. Diet has little effect on the hypercholesterolemia of hypothyroidism. It is restricted as an important aid in its control. Sources of visible fat must be restricted, except the vegetable oils which contain phytosterol, because it is not utilized in the human economy. Special care must be given to meats whose content of invisible fat is high, as much of this fat is cholesterol. Glandular meats are completely eliminated from the diet. Egg yolks are restricted. Egg white is permitted. Whole milk is replaced with skim milk. All cheese avoided except cottage and pot cheese.

2) Thyroid stimulation. Deficient thyroid activity is stimulated to normal by use of thyroid gland prescribed to tolerance, guided by basal metabolic rate, blood cholesterol and differential white cell count. The highest tolerated thyroid dose may be continued indefinitely.

3) Weight control. Overweight is the rule in this syndrome. The dietary program, in such cases, is similar to that followed in the treatment of obesity: High protein, low caloric, low cholesterol.

4) Psychotherapy. Considerable psychotherapy is needed in many of these patients. When atonia of the sympathetic nervous system is found, treatment is directed toward its correction. As thyroid function is restored and emotional instability is dispelled, the patient-physician relationship is gainfully achieved.

5) Bio-oxidation. As the study progressed, it became increasingly apparent that the underlying biochemical dysfunction was a matter of lowered bio-oxidation. Greater emphasis was then given to stimulating intermediary metabolism. This included the fostering of increased aerobic and anaerobic bio-oxidation. The drugs of choice for this objective include the enzymatic functioning B vitamins given in proper proportion as suggested by Cayer (14). These are combined with supplementary amino acids now known to be necessary for building the B vitamins into appropriate enzymes and conjugated further with catalytic metals. Intensive treatment with such prescriptions gave prompt results.

6) Lipotropic agents. Suitable lipotropic agents are necessary aids in affecting the reduction of blood cholesterol levels. Choline, inositol and methionine were made part of the B complex formulation. A new lipotropic agent is without conspicuous effect on the total lipids of the blood, but is selective in lowering blood cholesterol. It is an unsaturated fatty acid split away from lecithin derived from sunflower seed oil. ("Povon" 9, 12-octadecadienoic acid*)

7) Supportive measures. Liver extract and iron are given when indicated. Vitamins supplant restrictions in diet.

*John Peck Laboratories, Inc., New York, N. Y.

BRIEF ABSTRACTS OF CASE HISTORIES

Randomly selected case histories from the series of patients disclose the symptom triad mentioned,—Hypothyroidism, hypercholesterolemia and occult lymphocytosis on their initial visit as follows:—

Case 11: M. Age 58, excessive fatigability. Obese. BMR—29%. Blood cholesterol, 331 mgs. Lymphocytic index, 1.66.

Case 23: F. Age 32, headache, insomnia, joint pain, constipation, obese. BMR—15%. Blood cholesterol 292 mgs. Lymphocytic index, 1.83.

Case 39: F. Age 54, precordial pain, dyspnoea, exhaustion, insomnia. BMR—16%. Blood cholesterol, 328 mgs. Lymphocytic index, 1.83.

Case 52: F. Age 45, emotional instability, headache. BMR—20%. Blood cholesterol, 387 mgs. Lymphocytic index, 1.63.

Case 68: M. Age 37, tinnitus, vertigo, progressive deafness. BMR—25%. Blood cholesterol, 282 mgs. Lymphocytic index, 2.00

Case 82: F. Age 45, exhaustion, headache, incipient osteo-arthritis. BMR—14%. Blood cholesterol, 244 mgs. Lymphocytic index, 1.53.

Case 93: M. Age 46, rapid gain in weight, painful joints. BMR—23%. Blood cholesterol, 294 mgs. Lymphocytic index, 2.10.

Case 106: M. Age 60, history of very low blood pressure. Hypertensive past five years. Dyspnoea, myocardial changes, paroxysmal tachycardia. BMR—30%. Blood cholesterol, 294 mgs. Lymphocytic index, 1.96.

Case 120: F. Age 49, painful joints, fatigue, constipation, headache. BMR—15%. Blood cholesterol, 282 mgs. Lymphocytic index, 1.50.

Case 131: F. Age 53, gall bladder disease, headache, osteo-arthritis. BMR—19%. Blood cholesterol, 308 mgs. Lymphocytic index, 1.56.

Case 140: F. Age 16, frequent sore throat, fatigue, constipation, painful joints. BMR—25%. Blood cholesterol, 257 mgs. Lymphocytic index, 1.70.

Case 156: F. Age 54, exhaustion, headache, constipation, indigestion, marked hypotension. BMR—22%. Blood cholesterol, 284 mgs. Lymphocytic index, 1.23.

Case 167: F. Age 22, indigestion, constipation, obese, hypotensive. Blood cholesterol, 286 mgs. BMR—20%. Lymphocytic index, 1.51.

Case 182: M. Age 56, precordial pain, headache, myocardial damage, obese. BMR—18%. Blood cholesterol, 282 mgs. Lymphocytic index, 2.03.

Case 193: M. Age 42, insomnia, osteo-arthritis, obese. BMR—19%. Blood cholesterol, 393 mgs. Lymphocytic index, 1.73.

Case 201: F. Age 54, arthritis 15 years, headache, indigestion, hypotensive, osteo-arthritis. BMR—20%. Blood cholesterol, 276 mgs. Lymphocytic index, 1.77.

Case 215: F. Age 52, Headache, constipation, osteo-arthritis, hypotension. BMR—13%. Blood cholesterol, 214 mgs. Lymphocytic index, 1.66.

Case 235: F. Age 23, exhaustion, headache, indigestion, hypotensive, underweight. BMR—15%. Blood cholesterol, 254 mgs. Lymphocytic index, 2.33.

Case 240: F. Age 70, precordial pain, fatigue, vertigo, osteo-arthritis, obese. BHR—25%. Blood cholesterol, 273 mgs. Lymphocytic index, 2.53.

Case 272: F. Age 39, headache, obese, constipation, hypotensive. BMR—19%. Blood cholesterol, 275 mgs. Lymphocytic index, 2.00.

Case 278: F. Age 44, Obese, fatigue. BMR—20% Blood cholesterol, 366 mgs. Lymphocytic index, 1.90.

SUMMARY

Degenerative diseases are primarily those in which mesodermal structures are at fault; and lymphocytes are primarily mesodermal structures.

A poverty of leucocytes is a prominent consistent finding in the hypercholesterolemia of hypothyroidism. This depletion of leucocytes deprives the body of an important defense against disease. It has also been demonstrated that the lymphocytes are a factor in the production of antibodies.

In 280 hypercholesterolemia patients with hypothyroidism, a pattern of common clinical symptoms presented, 1) Undue exhaustibility. 2) Nervous tension. 3) Increased reaction to the histamine test. Dermatographia was generally demonstrable. Some manifestation of gastro-intestinal dysfunction was present in practically all cases, and constipation was a common complaint.

An impressionable number of cases were, at one time, treated for sinusitis and/or migraine. Rarely did an x-ray examination confirm sinus disease. Post nasal drip was an almost universal finding, generally accompanied by a perennial sub-acute rhino-pharyngitis.

From the consistency of these complaints, it is apparent that lymphocytosis is associated with histamine hypersensitivity, reduced resistance to infection and lowered recuperative powers. It may therefore be concluded that:

1. An occult lymphocytosis develops in cases of hypercholesterolemia with hypothyroidism.

2. A common pattern of symptoms is presented.

3. Thyroid activity is reflected in cellular differentiation expressed by selective increase in mesodermally derived lymphocytes.

4. Corrective therapeutic measures gave gratifying results with a more normal re-equilibration of the white cells, a drop in the blood cholesterol (The mean blood cholesterol level in this study is 300 mgs. of total cholesterol), and a correction of the basal metabolic rate to the normal levels.

5. A newer cholesterotropic drug, derived from the lecithin of sunflower seed oil, "Povon", is helpful in specifically lowering blood cholesterol which fails to respond to the more usual lipotropic factors,—choline, methionine and inositol.

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ABSTRACTS ON NUTRITION

FRAZER, A. C.: *Fat metabolism and the sprue syndrome.* (Brit. Med. J. Oct. 8, 1949, 770-773).

Tropical sprue, non-tropical sprue and the celiac syndrome in children are somehow related, and while recovery is the rule in the first, it is rare in the two latter. Defective fat absorption is an essential part of the sprue syndrome, and is due to a defect in particulate absorption. One intermittent characteristic, e. g., transient deficiency syndromes, may be due to the overgrowth of intestinal bacteria high in the gut. In non-tropical sprue and the celiac syndrome, Frazer thinks some enzyme is lacking which, if present, would assist absorption of fat particles. In tropical sprue perhaps dietary faults are of etiological significance.

RAPER, H. S.: *Fat absorption and some of its problems.* (Brit. Med. J. Oct. 1, '49, 719-724).

We actually do not know what happens to the whole of the fat absorbed after any given meal. The pumping action of the villi probably causes fat to enter the central lacteals. Petroleum, so different chemically from fat, is not absorbed at all. Probably about one-third of ingested fat passes directly into the blood stream. Phosphates may play a part in fat absorption. Lipolysis apparently is not essential for fat absorption; both neutral fat and fatty acid can be taken up by the intestinal cells, but are afterwards treated differently. Chylomicron counts are only helpful qualitatively. Emulsification assists absorption, and bile is important in their digestion and absorption, but bile is not essential for the absorption of very fine emulsions. In steatorrhea, there is no evidence of a selective failure of fat absorption, for there is a general impairment of absorption. The administration of yeast extract favorably influences fat absorption in tropical sprue.

MCCANCE, R. A.: *Serum cholesterinases in undernutrition.* (Proc. Roy. Soc. Med., 43, 4, 272).

Since the general level of serum proteins was known to fall in undernutrition, and since the serum enzymes are probably specific proteins, McCance et al. (Nature, 161, 56, 1948) decided to estimate the activities of these enzymes in the serum of undernourished persons. Serum cholesterinase was found to be low, and the activity rose as the plane of nutrition improved. Probably the level of cholesterinase in the serum is a reflection of the nutritional state, although the normal range is wide.

YUDKIN, J.: *Food and mankind.* (Brit Med. J., May 13, 1950, 1101-1105).

Yudkin, professor of physiology at the University of London, states that the world food situation has always been serious, but will become increasingly critical during the balance of the present century when the population of the world, now 2 1/3 billions, is expected to reach 3 billions. A two-fold increase in food is needed now to adequately feed humanity. Some progress may be made through prevention of wastage, through control of soil erosion and by improved agricultural techniques. He favors birth control but realizes how difficult it is to inculcate the practice among the lower social levels. He says possibly the solution lies in the discovery of new principles of birth control. In a country like Britain, which must import most of its food, and in which the external demand for its manufactured products is decreasing, a continuation of price controls and food rationing is imperative. The article is a good review of the world food conundrum, though it does not profess to offer any panaceas.

MORRISON, L. M. AND JOHNSON, K. D.: *Cholesterol content of the coronary arteries and blood in acute coronary artery thrombosis.* (Amer. Heart J., 39, 1, 31-34).

The average cholesterol content of the coronary arteries in a group of patients who died from coronary thrombosis was found to be four times as great as the average cholesterol of the coronary arteries in a comparable control group. Hypercholesterolemia was found in most of the patients who died of coronary thrombosis, as compared to a normal blood cholesterol average in the control group. These findings suggest a disturbance in the lipid metabolism as a factor in the pathogenesis of atherosclerosis.

STONE, H.: *Intravenous iron therapy.* (New Zealand Med. J., 48: 268, 614-616).

A case is presented of a woman of 50 with chronic microcytic hypochromic anemia and achlorhydria, in whom excellent results were obtained by the intravenous administration of saccharated iron oxide. The author points out that in health very little iron is absorbed from the G. I. tract and that in achylia, the absorption is extremely poor. His case was one of Plummer-Vinson syndrome. (Unfortunately localized thromboses occurred at the sites of injection). He points out that two kinds of anemic patients require intravenous iron,—(1) Those who show no response to iron by mouth, (2) Those who cannot tolerate it.

VEGHELYT, P. V., KEMENY, T. T., POZSONYI, J. AND SOS, J.: *Dietary lesions of the pancreas.* (Am. J. Dis. Child, 79, 4, 658-665).

It was observed in infants that the first sign of the disease characterized by fatty liver and edema, caused by lack of animal protein, was the cessation of pancreatic function. Histological examination revealed fragmentation of the pancreatic parenchyma, cyst-like dilatation of acini and diffuse cirrhosis. Rats were fed diets in which yeast or glue was the only source of protein. Dissociation of the excretory system of the pancreas, cystic changes and cirrhosis were seen to develop. Addition of casein, or in the glue diets, of methionine, exerted a protective action. The relation of the pancreatic changes to those in the liver and their possible similarity to cystic fibrosis are discussed.

PETERS, J. P.: *Malnutrition and edema.* (Nutrition Reviews, 8, 2, 33-36).

Famine victims with edema and serum albumins ranging from 1.03 to 1.64 per cent, recovered from the edema when, as a result of feeding, the serum albumin rose to 2 per cent. However, in some cases of experimentally produced hunger edema in human subjects there were found only very slight diminutions of serum albumin levels in persons suffering from extreme emaciation as a result of anorexia nervosa. While malnutrition edema cannot be correlated with the degree of hypoalbuminemia, it is regularly relieved by giving adequate amounts of protein, and the discharge of edema is accompanied by a rise in serum albumin. The administration of the sodium ion causes edema to appear at unusually high concentrations of albumin. The correlation among serum albumin, hypoalbuminemia and edema can be established only under the most carefully standardized conditions. The reduction in blood protein following injury, shock or infection is poorly understood. The "reaction to injury" appears also to involve lipids and serum precipitable iodine.

REILLY, W. A.: *The treatment of obesity in childhood.* (Amer. Pract. and Digest of Treatment, 1, 3, 228-234).

Reilly believes that among children over six years of age, at least 20 percent are obese and should be treated. In deciding whether or not obesity exists, one must take into consideration not only height, age and weight but also "body build," and for this purpose Pryor's or Stuart's tables are advisable. Even infants, if they are obese ought to be treated. He presents dietary tables suitable at various ages. The treatment is almost entirely dietary. Success is obtained in 75 percent of cases. An important factor is the physician's ability to persuade the child of the need and the good results of treatment.

WAIFE, S. O.: *Difficulties in the diagnosis of malnutrition.* (Amer. Pract. and Digest of Treatment, 1, 3, 225-227).

Waife shows that the word malnutrition has naturally been too loosely employed without proper reference to its exact meaning in individual cases. We need to state what particular nutrients are being ingested in insufficient quantities, whether this involves a vitamin, several vitamins, proteins, water and

so on. Malnutrition may be caused by inadequate feeding or decreased bodily reserves, and may result in functional impairments (e.g. dark adaptation) or anatomic lesions particularly in the skin and mucous membranes. Because a person is fat does not mean that he is well-nourished for he may show a calcium deficiency. Waife pleads for greater definition and specificity in our descriptions of so-called malnutrition, so that particular nutrients are named and the length of time involved in the deficiency stated.

POE, W. D.: *The effect of endogenous insulin on gastric function: a clinical study.* (Annals Int. Med., 32, 2, 279-283).

The author studied 50 patients with hyperinsulinism particularly from the standpoint of gastric acidity and gastric motility. Generally, it was found that there was an increased gastric secretion and motility, as well as increased gastro-intestinal symptoms in persons with spontaneous hypoglycemia although these could not be accurately correlated with the blood sugar readings. The author feels that gastric function is largely dependent on carbohydrate metabolism with its influence on the vagus apparatus.

GILDER, S. S. B.: *Symptoms and signs of experimentally induced vitamin deficiencies in man.* (Brit. M. J., Feb. 11, 1950, 341-345).

An extensive search of the literature showed that vitamin A deficiency is hard to induce in healthy adults and the symptoms are trivial. In experimentally induced thiamine deficiency we find fatigue, anorexia, nausea, vomiting, peripheral neuritis, mental changes and cardiovascular effects. Riboflavin deficiency may lead to cheilosis but this is uncertain. The exact results of nicotinic acid deficiency are not yet known. (The author does not feel that pellagra always results from nicotinic acid deficiency). Pyridoxin deficiency may be associated with albuminuria, mental changes and lymphocytosis. Vitamin C deficiency leads, after an interval of several months, to perifollicular hyperkeratosis and later to petechial and perifollicular skin hemorrhages, although gum changes are slight.

EDITORIALS

THERE ARE NO PAT ANSWERS

UNESCO and FAO (respectively, United Nations Educational, Scientific and Cultural Organization and Food and Agricultural Organization), in association with the U. S. National Commission for UNESCO, the FAO Inter-agency Committee of the U. S. Government, the Department of Agriculture and a number of national private organizations representing farm, labor, consumer and other interests, have issued a brochure (Dept. of State Publication 3726) entitled *Food and People*, which is unquestionably of importance. Here we find the following solemn words,—"There is not enough food for all. Only one-third of the world's people get enough of the right kind of food and they consume three-fourths of the world's food supply. One half of the human race actually goes hungry, and famine and starvation still stalk the earth, as in ancient times. Disease, low efficiency, social tensions, and political and economic crises, in many areas, reflect the scarcity of food."

In the past ten years the human race has added 200 million members and every day the global population increases by 55,000. The somewhat hopeful note is that science has learned how to raise food production to levels undreamed of a generation ago. The State Department's brochure frankly admits there are no easy or obvious solutions to this problem with which the human race is faced. Much has still to be learned about where shortages exist and the nature of these shortages; what can be expected from improved agricultural methods in these areas; how waste can be cut down; how farmers are to produce the right crops for a "hungry world"; and so forth.

Obviously, the issuance of this pamphlet "Food and People" is primarily to awaken in the American public a consciousness of the distressing situation obtaining in world-wide nutrition. It is unlikely that any exaggerations have been made or that any political motive is involved. It appears to be the hope of UNESCO, and the State Department, that broad discussion of these involved problems can be stimulated throughout the United States. That, in itself, would serve as a useful introduction. Yet, it is equally plain that, as of the present moment, there exists no optimism among those whose positions should fit them to know the truth.

As this Journal has previously stated in its Editorials, we do not believe that any ready panacea exists for combatting global malnutrition. We believe that *sectional* solutions are possible and that these must be tied in with proper military preparedness to meet emergencies. The North Atlantic Pact is a beginning and the participating nations should primarily examine and perfect the nutritional status of their own populations before expending their substance elsewhere. That much seems obvious.

THE MEDICAL STRUGGLE IN INDIA

Medicine in India finds itself in a unique state of confusion. This is due to two important factors,—the poverty of rural areas and the coming of Independence. No sooner had British control been relinquished in India than certain forces in her new government advocated a return to the indigenous systems of medicine, particularly Ayurveda. This ancient system of healing extends back possibly 4000 years into the indistinct periods of the country's history and possesses few virtues likely to be acknowledged by anyone trained in modern, scientific methods. However, it is advocated today by many Indian scholars who, attracted by its philosophical and religious aspects, honestly believe it superior to scientific medicine. Its adoption also is favored by those short-sighted officials who think that because Ayurvedic services and drugs are cheaper, they should be employed for the benefit of the millions of poverty-ridden persons, especially in the rural districts of India. Finally, there exists throughout India a rather complete revulsion against Western civilization as a whole, and a determination to cast the future of this numerous people solely in terms of Eastern genius.

The Indian Medical Association of course understands that a return to indigenous systems of medicine would be a tragedy and, in the long run, extremely expensive in rupees and in human life. Proposals to form a merger of Ayurveda and scientific medicine likewise are considered endlessly confusing and practically impossible. The Association contends that West-

ern medical education must be maintained and extended with strict attention to licensure of physicians and pharmacists. They raise no objection, however, to a historico-experimental investigation of certain aspects of the ancient systems, with eventual incorporation into the modern practice of medicine of those procedures and those indigenous drugs which can be scientifically shown to possess sufficient virtue. Undoubtedly, The Indian Medical Association has adopted the only rational attitude possible under the circumstances, but it is not yet entirely clear that the Association will win an early or decisive victory over the reactionary elements in government and elsewhere. The religious and philosophical systems of India are among the most impressive in the long story of humanity's evolution, but when applied to a curative practice, they fail to impress those physicians in India who have had intimate experience with chemical and hormonal therapies.

BOOK REVIEWS

Peptic Ulcer. A. C. Ivy, M. I. Grossman and William H. Bachrach. 1144 pages, 137 illustrations, 210 tables. Blakiston Company, Philadelphia 5, Pa., 1950, $14.00.

Never before, in the history of medical literature, has so much been said in such succinct form, in a book of 1200 pages, or in any book, on the subject of peptic ulcer. For once, the subject is completely covered in a manner highly pleasing to the physician, the scientist, and the surgeon alike. It is an exhaustive resume of the pathogenesis, diagnosis and treatment of peptic ulcer based both on clinical and experimental findings. The book contains 4 Parts, 21 chapters, and provides a condensed summary for each Part. It is considered that peptic ulcer results from a combination of many causes, of which acid-pepsin secretion, local injury to the mucosa and "emotogenic" influences are the chief. Personality "profile" studies are considered less valuable than had been expected. Constitutionality studies have not been of much practical help. The authors do not feel that most ulcer patients manifest a characteristic personality pattern or conflict-situation. They consider that Alexander did not prove his concept of "repressed oral-receptive cravings" as the basic conflict-situation in peptic ulcer, because he did not study enough cases analytically. Only a few pages are devoted to depth psychology. Sullivan and McKell in their recent book, *Personality in Peptic Ulcer*, are in perfect agreement with Ivy in their assessment of Alexander's hypothesis. In defence of Alexander, a reading of his recent book, *Psychosomatic Medicine*, shows that he, Alexander, also deprecates profile studies, and does not postulate a definite or fixed "conflict-situation" in peptic ulcer. The conflict-situation may be anything in the world, but the *regressive tendency*, in which the ego seeks satisfaction, is the real basic process. This is a matter for psychoanalysts to help settle, because physiologists cannot do much about it. Ivy, et al. have avoided much mention of the effects of psychotherapy on the healing of ulcer. In the present stage of our "knowledge" of the pathogenic processes in peptic ulcer, this is not a serious omission. The authors have placed the profession under definite obligation by writing the most perfect book on Peptic Ulcer to date. It is not only encyclopedic, but very readable and helpful.

Psychosomatic Medicine. Franz Alexander, M. D., 300 pages. W. W. Norton and Co., Inc., New York, 1950, $4.00.

Alexander insists that psychological factors influencing physiological processes must be as minutely examined as is customary in the study of physiological processes. The use of such general terms as anxiety, tension and emotional imbalance are too nonspecific. Each emotion must be broken down into its components and this can only be done by the application of dynamic psychology. Psychological processes must be viewed as being actual physiological processes, but capable, as the others are not, of subjective perception and verbal report. The aim of modern scientific medical psychology is to attempt to place on a scientific basis the psychological effect of the physician upon the patient. The psychoanalytic method, particularly, supplies an efficient technique for this purpose.

The author takes serious note of the resistance of practitioners to openly admitting the importance of the *psyche* in medicine, while they concurrently apply, with intuitive skill, psychotherapeutic methods. Alexander is no visionary. He is rather a rank "materialist", if that word any longer has a meaning, for he contends that the various subjective phenomena are merely the reflections of physiological processes. Alexander does not seem to feel that "personality profile" studies have given results sufficiently consistent to constitute an indispensable discipline. What actually matters, from a practical standpoint, is the precise emotional conflict of the individual patient and how the patient reacts to it. His remarks on the psychological elements in gastrointestinal disturbances are particularly interesting. While most persons today have accepted Alexander's original explanation of the frequent emotional basis of digestive symptoms, not everyone is convinced, as Alexander in this book is convinced, that the regressive element always is present if carefully looked for.

Possibly the present volume is the most direct and least apologetic of all the books yet written on the title subject. It deals consistently with depth psychology, a fact which narrows the ultimate conflicts to a comparatively few types. Just how these simple "depth" data in their many combinations and permutations become somatically expressed in so wide a variety of manifestations is the real problem for the clinician, and Alexander here does much to simplify it. *Psychosomatic medicine* is a 'key' book in that it succeeds in giving the subject a slightly new, more psychological and more direct orientation than previously has obtained in this difficult aspect of medicine.

Practice of Medicine. Jonathon C. Meakins, 1558 pages. The C. V. Mosby Company, St. Louis, 1950, $13.50.

In the Fifth Edition of Meakins' well-known *Practice of Medicine*, the section of psychiatry has been replaced by one on *psychosomatic medicine*, a term which Meakins does not like but consents to use, for lack of a better term. Peterson's chapter on the nervous system, which is possibly the best short work on neurology in existence, has fortunately been retained, although Peterson himself has passed on. There is a very satisfactory new chapter on chemotherapy and antibiotics. Many necessary minor alterations have been made elsewhere in the text. Writing a text book on Practice has become more difficult than ever before, because of the increase in specialized techniques. As Meakins states, many of these newer methods are now employed solely in large metropolitan clinics, but must not be omitted from the text. The reviewer has read this as well as previous editions of Meakins' *Practice of Medicine* and has found it an exceptionally readable and valuable book. Meakins constantly keeps the problems of the general practitioner in mind. The Fifth Edition is the best edition.

GENERAL ABSTRACTS OF CURRENT LITERATURE

ALEMAN, STEN. *Jejuno-gastric intussusception, a rare complication of the operated stomach.* Acta radiologica 29, 5, 383. May 1948.

The author reports a case of the roentgenological findings of a jejuno-gastric intussusception in a case previously subjected to a Billroth II stomach resection. The typical roentgenologic changes are those of visualization of Kerkerings folds inside the stomach near the gastro-jejunostomy. The clinical picture of this condition is described which, judging by the scanty literature on this subject, is very rare. The probable etiology and origin of the intussusception are discussed.

Franz J. Lust.

ESSENSON, LAWRENCE AND GINZBURG, LEON. *Volvulus of the sigmoid.* Am. J. Surg. 77, 2, 240. Feb. 1949.

Eight cases of acute sigmoid volvulus are presented from the surgical service of Harlem Hospital (New York City). In all 8 cases the diagnosis was made preoperatively by a correlation of the history, physical signs, and the plain roentgenograms of the abdomen taken in three positions suggested by the authors. By direct examination of the patient alone it was impossible to differentiate this condition from other types of acute intestinal obstruction. In the presence of any acute intestinal obstruction it is highly important to consider the presence of volvulus of the sigmoid. It is most often mistaken for acute obstruction of the left colon due to a new growth. It is to be remembered that the same principles of treatment do not apply to a sigmoid volvulus as to other obstructive lesions of the left colon because of the presence of an obstructed closed loop of bowel. Plain roentgenograms of the abdomen clearly demonstrated the presence of sigmoid volvulus in all cases reported by Essenson and Ginzburg. The characteristic "bent inner-tube" effect is demonstrated and other confirmatory x-ray features are pointed out. The therapy for acute volvulus is immediate operation with the object of untwisting the obstructed loop and the insertion of a rectal tube for decompression. If the blood supply to the twisted loop has been compromised, an exteriorization procedure is indicated.

Franz J. Lust.

WAGGONER, CHARLES M. AND LEMONE, DAVID V. *Clinical and roentgen aspects of internal biliary fistulas.* Radiology 53, 1, 31. July 1949.

In the twelve reported cases, the clinical findings were not consistent. Only cases due to a malignant growth presented a palpable mass. Scout films of the abdomen played an important role in diagnosis, revealing abnormal air patterns in all cases involving the gallbladder (ca 70% of this series). In cases of cholecystocolic fistula, the air patterns were adequate for the final diagnosis; in cholecystoduodenal fistulas such patterns were less marked and usually sufficient only for preliminary conclusions. Diagnostic air patterns on scout films were not observed in choledochal fistulas or those associated with malignant growths. All fistulas were easily demonstrated by barium studies of the g-i tract, with the exception of those blocked by a malignant mass or perforating calculus. Persistent duct obstruction or failure to pass a perforating calculus apparently maintains the patency of fistulas involving the duodenum. With involvement of the colon, severe secondary infection is an added factor for persistent fistula.

Franz J. Lust.

WILLARD, J. H.: *Cardiac symptoms secondary to gastrointestinal tract disturbances.* Amer. Pract. & Digest. Treat. 1, 4, 376-380.

Willard presents a lucid review of certain gastrointestinal conditions which are at times capable of producing angina, disturbed cardiac rhythm and cardiographic alterations of a transient nature. He points out that sometimes during an attack of angina pectoris, the esophagus has been seen under the x-ray to go into spasm, and other observers have noted intense gastrospasm in association with an anginal attack. It appears that anything causing either spasm or dilatation of the esophagus may produce anginal pain, with or without cardiographic changes. He refers to the work of Chester Jones who showed that esophageal hiatus hernias, particularly the small ones which so often escape x-ray detection, frequently give rise to anginal-type pain. Gallbladder disease may be responsible by vago-vagal reflex, for substernal pain. Such attacks may be abolished by atropine in sufficient doses. Even negative T waves in lead I may become normal following removal of a diseased gallbladder, and in cases of doubt a calculous gallbladder should be removed, provided cardiac decompensation has not taken place. In cases in which the blood potassium has been lowered as in diabetic acidosis or in protracted vomiting from any cause, we may find such cardiographic alterations as prolonged PR interval, depression of the ST segment, and negative T waves. (Willard does not include those cases of cardiac decompensation which become reversed by the successful treatment of an associated hepatic cirrhosis.)

FRANDSEN, EMIL. *Gastric achylia and so-called B-hypovitaminotic symptoms in cardiac disease.* Acta Me. Scand. 135, 6, 381. Oct. 1949.

In nearly 500 hospital patients the incidence of histamine-refractory achylia was found in 9% of the cases. Cardiac disease was ascertained in 118 patients, among whom gastric achylia was found in 33, i. e. in 27.9%. On sex and age distribution of the material, achylia is found not to be more frequent in cardiac patients than in the rest of the material. Among 24 decompensated cardiac patients histamine-refractory achylia was found in 12, hypochylia in 5, and normal acid secretion in only 7. A majority of these patients belonged to the age class of 50-80 years. In these age groups the frequency of achylia appears to have a tendency to increase as compared to the control material. The frequency of achylia seems to be dependent upon the duration of the decompensation.

B-hypovitaminotic symptoms are found to occur more frequently among the achylia patients, and with increased frequency among cardiac patients with achylia. Glossitis is found also among cardiac patients with normal acid values for the gastric secretion but more frequently among the decompensated cardiac patients. The B-hypovitaminotic symptoms appear to be of absorption nature. Glossitis is not only of achylic nature.

Franz J. Lust.

ISAAC, FRANK; OTTOMAN, RICHARD E.; AND WEINBERG, JOSEPH A. *Roentgen studies of the upper gastrointestinal tract in vagotomy.* Am. J. Roen. & Rad. Th. 63, 1, 66. Jan. 1950.

Eighty-three consecutive cases of vagus resection were studied roentgenologically. The postvagotomy studies included 75 patients at one week, 72 patients at one month, and 50 patients at 6 months. The changes found in the stomach after vagus resection are decreased peristalsis, delayed motility, and loss of tone with dilatation. Of those examined one week after vagotomy, 87% showed decreased peristalsis, 80% delayed motility, and 54% loss of tone. The tendency for these functions is toward gradual improvement. At 6 months, however, a rather large percentage did not return to normal: 48% in case of peristalsis, 41% in case of motility, and 33% in case of tone. The changes are found with equal frequency whether the operation has been performed by the thoracic or abdominal route and whether it is simple vagotomy or combined with gastroenterostomy. The tendency to return to normal, however, is greater after the combined operation than after simple vagotomy. A majority of those having demonstrable ulcer crater in the duodenal bulb before operation show a disappearance of the niche after vagotomy. In this series 42% had a crater before operation, but only 14% after vagotomy.

In the small intestine the most constant changes consist of dilatation of the duodenum and delay of the intestinal motility. Less constant alterations of small intestinal pattern include dilatation of the jejunum and ileum, segmentation, pooling and flocculation of the barium.

Franz J. Lust.

ROGERS, J. D., AND PRIESTLY, J. T.: *Cystic dilatation of the common bile duct: report of a case.* Staff Meet. Mayo Clin. 1949, 24, 23, 568-575.

Congenital cyst of the common bile duct, a rare disease, is described in a 64-year-old woman, the oldest patient to present this anomaly on record. Salient symptoms are palpable tumor, jaundice and pain. The establishment of the Roux-Y type of anastomosis between the cyst and the jejunum is offered as the most satisfactory method of surgical treatment.

HAWORTH, J. B. AND RAWLS, N. B.: *Prepyloric local gastritis.* Radiology 1949, 53, 5, 720-728.

The authors describe a form of gastritis limited to the antral area, and have collected 285 alleged cases of the disease. The x-ray indications consist of irregularities in the prepyloric area, particularly on the lesser curvature, often simulating the appearance of cancer, but disappearing after the proper treatment, which seems to be very much like that of ulcer,—bland diet, aluminum hydroxide, atropine, anti-histaminics (the latter being almost specific for the disease), discontinuance of coffee, tobacco and alcohol, and psychotherapy. In nearly half the cases the condition was associated with peptic ulcer and the authors think it may be a precursor of ulcer. The symptoms closely resemble those of ulcer, and the disease may possibly account for a large number of undiagnosed dyspepsias.

BLOOMENTHAL, E. D. AND BENDIX, R. M.: *Hemorrhoidectomy.* Illinois M. J. 1949, 96, 5, 311-314.

The authors describe an open technique for hemorrhoidectomy, in which the hemorrhoid is completely dissected out and in which nupercaine in oil is injected into the isolated external sphincter ani, under direct visualization. Post-operative spasm is eliminated and there have been no recurrences or septic complications in a series of 106 cases so treated.

WALDBOTT, G. L.: *Chronic Urticaria.* Harper Hosp. Bull. 8, 1, 10-15.

Waldbott makes a distinction between chronic urticaria in allergic persons and in non-allergic persons. In non-allergic individuals suffering from chronic urticaria there is much less personal and family history of allergy, no asthma, no gastrointestinal manifestations of allergy and no eczema; the eosinophile count is lower and the white blood cell count is higher than in allergic persons. Fever is associated with urticaria in non-allergic persons but not in allergic persons, and joint pains are much commoner. In non-allergic persons, drugs (especially aspirin) played, along with infections, the chief etiological role. It is emphasized that where the individual is allergic to foods, he improves promptly on a restrictive diet based on the intradermal skin tests.

KRIEG, E. G. M.: *Cold to the post-operative wound for controlling pain and other complications.* Harper Hosp. Bull. 8, 1, 6-9.

Krieg cites statistics which suggest that pulmonary atelectasis and urinary retention post-operatively are largely due to the use of narcotic drugs. Nerve blocking to relieve wound pain is effective but it is complicated and not without risk. The use of bare ice caps to the wound appears to serve the purpose well and permits a tremendous reduction in the amount of narcotic required post-operatively. The only problem in the use of the ice cap is to keep it filled with ice at night and to avoid putting a cover over the ice bag. He does not mention the danger of freezing the skin.

SZASZ, T. S.: *Factors in the pathogenesis of peptic ulcer.* Psychosomatic Med. Sept.-Oct. 1949. XI, 5, 300-303.

Szasz criticises the recent dog experiments of Mahl in which "chronic fear", (induced by strong electric shocks and the sound of a buzzer at unpredictable intervals) was found to have induced in most of the dogs an increased gastric acidity. Szasz takes the attitude that these dogs were not so much the subject of fear as of a massive disorganization of their behavior, and anyone reading Mahl's article would get this impression. The increased gastric secretion is thus explained as an evidence of *regression*. Szasz cites the formation of peptic ulcers in prematurely weaned calves and their cure by permitting the calves to continue on a milk diet, as evidence for the correctness of the psychoanalytic theory of peptic ulcer formation.

LING, C. C., CHENG, W. J. AND CHUNG, H. L.: *Clinical and diagnostic features of Schistosomiasis Japonica.* Chinese Med. J. July 1949, 67, 7, 347-66.

Depending upon the location of ova deposited in various tissues, schistosomiasis japonica, one of the most important parasitic diseases in China, shows the following forms,—dysenteric, periportal cirrhotic, splenomegalic, constitutional, respiratory, appendicular, intestinal obstructive, mesenteric vascular occlusive, abdominal tumor formation, cerebral, myelitic, gastric, uterocervical and some subclinical forms. Absolute diagnosis depends on finding the specific ova in excreta and tissues. Sometimes a normal appearing rectal mucosa will show the ova on biopsy. Tartar emetic is the treatment but is is dangerous in the presence of serious hepatic involvement.

MORETON, R. D., STEVENSON, C. A. AND YATES, C. W.: *Fictitious polyps as seen in double contrast studies of the colon.* Radiology, 53, 3, 386-393.

In using the barium enema combined with air insufflation, it is necessary, in the authors' opinion, to have the colon thoroughly cleansed beforehand by means of laxatives as well as simple enemas. Otherwise, artificial appearances, resembling polyps, will be found to occur in the colon films in about 25 percent of cases. Even the nature of the patient's diet as well as the type of lubricant used on the enema tip have a bearing on the production of these deceptive artefacts. Once such pictures are obtained there is no way to confirm or deny their reliability except to repeat the barium enema. A high roughage diet is likely to leave a deposit of undigested fibers in the colon, and these, as well as oil droplets may simulate polyps in the x-ray films.

GRACE, W. J., HOLMAN, C. W., WOLF, S. AND WOLFF, H. G.: *The effect of vagotomy on the human colon.* Gastroenterology 1949, 13, 6, 536-546.

The authors studied a 26 year old male patient with a large area of evaginated colonic mucosa, who was suffering from ulcerative colitis. Observations were made both before and after a bilateral supra-diaphragmatic vagotomy, performed for the alleviation of the colitis. The contractile activity, the mucus and lysozyme secretion were all quantitatively studied before and after the vagotomy. There was no evidence that the vagotomy altered the behavior of the colon or protected it from acute exacerbations of chronic ulcerative colitis. (Dennis has reported significant improvement in 14 of 25 patients on whom vagotomy was performed for ulcerative colitis). The authors feel that the anatomic basis for this procedure is not clear, for it is not certain that fibres of the vagus nerve actually reach the right colon.

CRANDALL, L. A.: *The absorption of barium sulfate and non-absorption of zirconium dioxide from the gastrointestinal tract.* Gastroenterology, 1949, 13, 6, 513-525.

The absorption of barium after the oral administration of barium sulfate was demonstrated by the administration of the radioactive Ba^{140} as a tracer, followed by the determination of the radioactivity of the rat carcass ash, and was confirmed by the spectroscopic determination of barium in the carcass ash of rats fed ordinary barium sulfate. Control studies using zirconium dioxide indicated that no detectable amount of the latter material was absorbed. Certain properties of zirconium dioxide invite consideration of the use of this substance in x-ray investigations of the gastrointestinal tract.

ROSENAK, B. D., MOSER, R. H. AND HOWELL, J. D.: *Chronic and recurrent infectious hepatitis: its relationship to cirrhosis of the liver.* (J. Indiana St. Med. Assn., Sept. 1949, 42, 9, 897-902).

The authors selectively criticise the various liver function tests as applied in the diagnosis of hepatitis and conclude that usually the history and clinical examination alone will yield the diagnosis. They discuss the possible role of chronic hepatitis in the pathogenesis of liver cirrhosis. The degenerative and fibrotic changes histologically noted in material obtained by needle biopsy in the course of protracted hepatitis favor such a causal connection. Two cases of this type are described.

SPATT, S. D. AND ROSENBLATT, P.: *The incidence of hypertension in portal cirrhosis: a study of 80 necropsied cases of portal cirrhosis.* (Ann. Int. Medicine, 31, 3, 479-483).

The authors show that the incidence of hypertension in patients with portal cirrhosis is significantly lower than in the general population, using blood pressure readings, heart weights, or both, as criteria, although at the present moment this lower incidence of hypertension is quite unexplained.

MORETON, R. D. AND YATES, C. W.: *The double-contrast study of the colon: a comparative study of barium sulfate preparations.* (Radiology, 54, 4, 541-547).

Only 2 barium sulfate preparations on the market have been made especially for study of the colon and are referred to as I-X Barium, Unflavored and Improved Stabarium. It was found that either of these gave better results than ordinary barium sulfate preparations in double-contrast study of the colon, neither were toxic, although both were more expensive. The manufacturers' names are omitted.

GOTTLIEB, C., CHU, F., AND SHARLIN, H. S.: *Perforation of a gastric ulcer associated with intracranial hemorrhage in a newborn infant.* (Radiology, 54, 4, 595-597).

The case is reported of an infant who presented a perforated gastric ulcer in association with intracranial hemorrhage on the second day of life. X-ray evidence of a gastric lesion and of free air in the peritoneal cavity led to laparotomy at which the perforated ulcer was located. The patient died on the fourth day of life of peritonitis. Autopsy revealed intracranial hemorrhage due to a tear of the tentorium. Reference is made to Cushing, who found that melena in infants may be attributable to an intracranial lesion, and that cerebellar disease was associated with peptic ulcer.

KIENLE, FRANZ AND KNUECHEL, FRITZ: *Liver damage in acute and chronic insufficiency of the heart.* Aerztl. Forschung 3, 23, 571. Dec. 10, 1949.

In a group of 72 patients with insufficiency of the heart and congestion of the liver, liver function tests were made. Compared with tests of congestion and other reactions of lability, the thymol-, kephalin-, and cholestonon-tests proved to be most sensitive and specific. 69% were positive, with 27% strongly positive. The degree of the disorder of the liver is demonstrated in several cases. In 12 cases examined by autopsy a constant relation between the degree of the histological alteration of the liver parenchyma and the deviation of the reaction from the normal could be found. The liver damage seems to be due to a diminution of circulation in the liver and the hypoxemia following it, with obstructed elimination of catabolites.

Franz J. Lust.

STROMBECK, J. P.: *Surgical treatment of ulcerative colitis.* Nordisk Medisin 1950, 43, 501.

Fifty-four cases of ulcerative colitis have been treated at the University Hospital, Lund, during the past eight years. Ileostomy was done in twelve of the cases, in five followed by subtotal colectomy. The restoration of normal-, salt- and protein balance is most urgent in fulminant cases. With improved after-treatment, and assuming the indications and technic to be correct, ileostomy is not as socially disabling as might be supposed. Colectomy is thought to be the only therapeutic measure sufficiently effective in progressive cases.

O. W. Husebye, Oslo.

ARONSSON, HUGO: *Complete prolapse of the rectum.* Nordisk Medisin, 1950, 43, 499.

Partial prolapse of the rectum, which involves only the rectal mucosa in adults is usually a sequela of hemorrhoids or ano-rectal incontinence. Complete rectal prolapse, on the other hand, involving all the layers of the rectal wall, is a disease in itself. The pathogenesis according to Moschcowitz and Graham is touched upon. Operation by the perineal route according to the methods of Rhen-Delorme and Mikulicz have given unsatisfactory results, with a high incidence of recurrences.

A report is presented of three cases of complete rectal prolapse which were surgically treated *ad modum* Moschcowitz and Graham with good results.

O. W. Husebye, Oslo.

HIRSCHBERG, FRITZ: *The bicarbonate test.* Nordisk Medisin. 1950, 43, 498.

The author points out the incongruity between subjective acid dyspepsia and objective superacidity or supersecretion. In this connection Katsch has introduced the term acidism for subjective acid dypepsia. Acidism includes cardialgia, heart-burn and acid regurgitation. Even though hunger pains and tardive pains react favourably to bicarbonate of soda, they are not included under the term acidism. This is due to the theoretical considerations.

Among the clinical symptoms of hyperacidity the author includes both hunger pains and all other discomfort which responds to bicarbonate. The bicarbonate test is far superior to all the gastric content tests for determining the nature of the discomfort not least because of the incongruity between subjective discomfort and objective findings. The bicarbonate test is a valuable aid in the differential diagnosis between primary and secondary acid symptoms. Among the causes of secondary acid symptoms are chronic appendicitis and colitis localized to the coecum and the ascending colon. Furthermore the bicarbonate test often affords a differential diagnosis between ulcer and coronary sclerosis, ulcer and enteritis, ulcer and cholecystopathy, and nervous and organic dyspepsia. The suggestive influence must be eliminated when evaluating the bicarbonate test.

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1. Sollmann, T.: A Manual of Pharmacology. Philadelphia, W. B. Saunders Co., 7th ed., p. 938.
2. Batterman, R. C., and Ehrenfeld, I.: *Gastroenterology*, 9:141, Aug., 1947.
3. Woldman, E. E., and Polan, C. G.: *Am. Jour. Med. Sc.*, 198:155, Aug., 1939.

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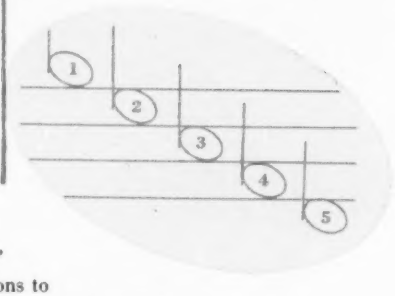

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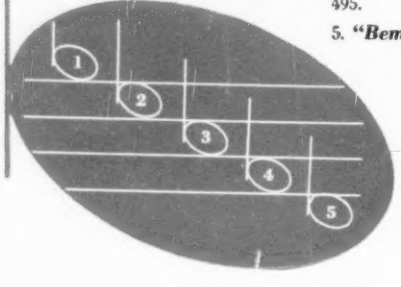

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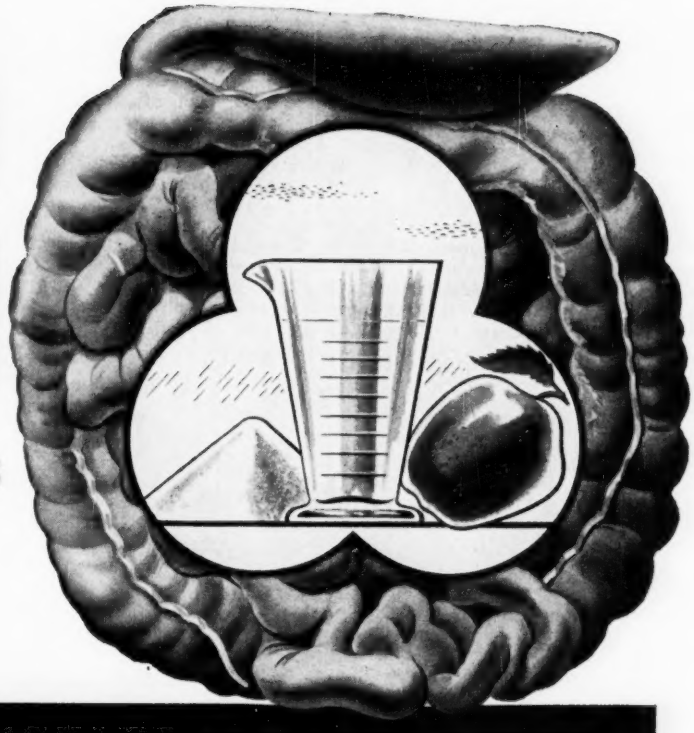

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*PB abbreviated designation for phenobarbital.
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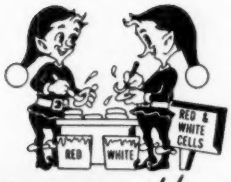
PRESENT HEALTH CONDITIONS IN ISRAEL

The appearance of Volume 1, 1950 of THE HEBREW MEDICAL JOURNAL (Harofé Haivri), inaugurates the 23rd year of its publication under the editorship of Moses Einhorn, M. D.

Written in Hebrew, with English summaries, the Journal is a contribution to improving the health of the new State of Israel, aiding as it does the development of Hebrew medical literature, and thus the newly established Hebrew University-Hadassah Medical School.

In the current number, a symposium is presented on various phases of disease and health in Israel. Among the articles of interest are "Orthopedic Problems in Israel" by I. Pulvermacher, M. D., "Fighting Deafness in Israel" by Ahron Schwarzbart, M. D., and "Kupat Holim—The Labor Health Service in Israel" by Moshè Rabinowitz, director of Kupat Holim in Tel Aviv.

In the section on Bible and Medicine, Dr. C. Genazzani presents a unique essay on "Pathological Symptoms caused by the Famine during the Siege of Jerusalem by Nebuchadnezzar, King of Babylon." In the section on Old Hebrew Medical Manuscripts, Dr. Zussmann Muntner of Jerusalem presents a historical article on "Ascites—A 10th Century Manuscript" by Yizchak Ben Shlomo Ha-Yisraeli. In

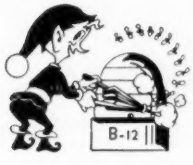


QUESTION: *How many red blood cells are replaced due to "wear and tear"?*

ANSWER: *Approximately 25 million a day in normal people*

When abnormal demands overtax the blood forming capacity of the body producing easy fatigability, sub-clinical anemia too often does not receive corrective treatment until more serious symptoms urgently demand attention.

Frequently more than just iron deficiency is involved. The patient does not respond to simple iron therapy and other factors must be added.



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LIQUID AND CAPSULES

addition, under the heading of Personalia, are presented biographical sketches on the life and works of Professor Hermann Strauss and Dr. Howard Lilienthal, noted American surgeon.

For more information write to THE HEBREW MEDICAL JOURNAL, 983 Park Avenue, New York 28, N. Y.

CARMETHOSE-TRASENTINE

A new combination of an antacid and antispasmodic is being issued under the name of CARMETHOSE-TRASENTINE by Ciba Pharmaceutical Products, Inc. Adding TRASENTINE to CARMETHOSE is in line with the latest therapy for hyperacidity and peptic ulcer.

CARMETHOSE-TRASENTINE provides relief of gastric discomfort and pain in cases where high acidity, hypermotility and spasm are factors in peptic ulcer, gastric neuroses, simple gastritis and other forms of gastric dysfunction.

Carmethose is the new antacid that aroused considerable interest at the American Medical Association Convention last summer. It forms a tenacious coating over the stomach lining and has all the advantages of the ideal antacid with none of the objections such as constipation, acid rebound or effect on the acid-base balance.

The TRASENTINE is held in prolonged contact with the mucosa and has a local anesthetic action, the duration of which is increased by its slow release from the adhesive, gelatinous vehicle, CARMETHOSE. TRASENTINE also acts on the parasympathetic nervous system and the local musculature to reduce spasm.

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The dosage of CARMETHOSE-TRASENTINE is two to four tablets taken four to six times a day, spaced between meals to coincide with the supposed peak of gastric acidity, and at bedtime. The tablets should be taken with a glass of milk or water and should not be chewed.

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*Choline Dihydrogen Citrate (Choline . . . 1 Gm.)**	*2.5 Gm.*
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SCHERING ESTABLISHES ANOTHER ENDOCRINE RESEARCH FELLOWSHIP

Another Research Fellowship in Endocrinology has been established recently at Rutgers University by Schering Corporation, pharmaceutical manufacturers of Bloomfield, New Jersey. According to Dr. James H. Leathem, endocrinologist and staff member of the New Jersey University's Bureau of Biological Research, the grant valued at $2300 is intended for the support of fundamental research by graduate students in the field of steroid hormones. The Bureau of Biological Research is a research agency of the State University. It was established in 1936 to facilitate cooperative research in the several fields of biology.

Mr. Francis C. Brown, Schering president, stated that at Rutgers the new Schering grant will facilitate study of several important but unsolved problems, including the relationship between normal steroid hormone functions and the protein metabolism of the body. Further research is being done on the effects of steroid hormone compounds upon the reproductive system. The effect of the androgenic hormones on fertility is also under study.

SCIENTISTS DISCOVER BETTER PAIN-KILLERS

Three new local anesthetics, ortho-substituted procaine derivatives, were described recently for the first time by Dr. E. P. Luduena, of the

In palatable liquid dosage, it is now possible to provide complete and effective medical protection for the peptic ulcer patient.

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Average dose: one to two teaspoonfuls two hours after meals and at bedtime.

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ALZINOX TABLETS with Phenobarbital (1/4 gr.) and Homatropine Methyl Bromide (1/100 gr.)
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staff of the Sterling-Winthrop Research Institute, Rensselaer, N. Y. He was speaking before the American Society for Pharmacology and Experimental Therapeutics, a section of the Federation of the American Societies for Experimental Biology, meeting in Convention Hall here.

In a paper prepared for presentation before the group, Dr. Luduena said two of the new drugs appeared in tests on laboratory animals to be "more potent than pontocaine and to produce less local irritation." The three drugs are now known only by their laboratory numbers, WIN 3459, WIN 3706, and WIN 4069.

Laboratory experiments lead to the belief all three may be more effectively used for the surgical purposes for which pontocaine and novocaine are now employed, according to Dr. Luduena. Clinical evaluation is not yet complete, however he pointed out. So far, one, WIN 3459, has been submitted for clinical trial.

The drugs were first synthesized by the Institute's chemical division a number of years ago. The discovery was the outgrowth of work being undertaken on para aminosalicylic acid, an active agent in the treatment of tuberculosis. A paper on the chemistry prepared by Dr. R. O. Clinton, Dr. S. C. Laskowski, Mr. U. J. Salvador and Mrs. Mary Wilson of the Institute staff will shortly appear in the Journal of the American Chemical Society.

NOTICE
MEDICAL ILLUSTRATOR'S DIRECTORY AVAILABLE

The Directory issue of GRAPHICS, the official publication of the Association of Medical Illustrators, contains the name, address, training, professional experience and reference to major published work of each member. Other information pertaining to the profession is included.

The journal, to be issued on June first, will be available to those requiring medical illustration service, and will be sent, free of charge, upon request to the Editor, Miss Helen Lorraine, 5212 Sylvan Road, Richmond 25, Va.

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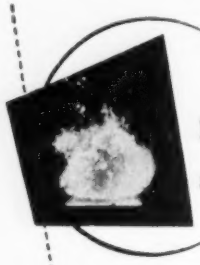

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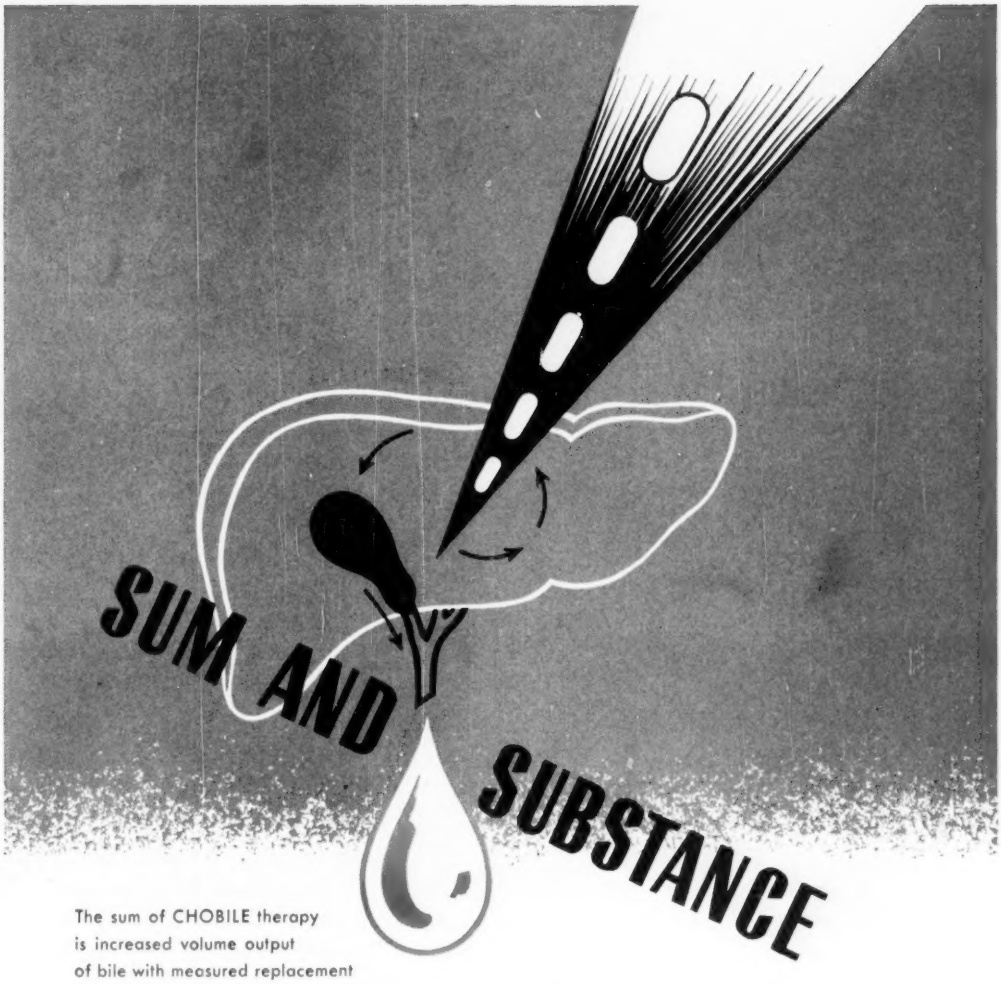

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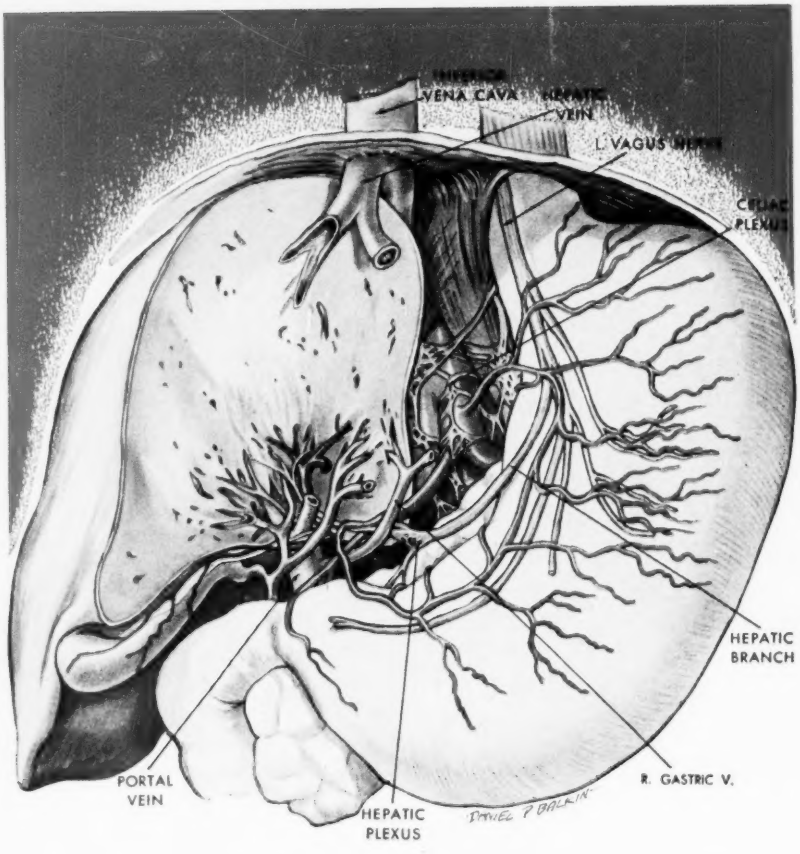

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